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Synthesis and Characterization of Carbon-Bridged (1(n))(2,6)pyridinophanes.

Young Je Joo
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The Louisiana State University and Agricultural and Mechanical Col., 1987

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SYNTHESIS AND CHARACTERIZATION OF CARBON-BRIDGED $[1_n](2,6)$PYRIDINOPHANES

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
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Doctor of Philosophy

in

The Department of Chemistry

by
Young Je Joo
M.S., Washington University, 1982
December, 1987

To Ihn-Sook, Hee-Jung, and Laura

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ABSTRACT

Pyridine-containing heterophanes, which possess a rigid non-flexible framework, similar to that of porphyrin backbones, are ideal structures to probe the electronic and/or steric effects within a highly electron-rich cavity. The syntheses of hetero-macrocycles incorporating the 2,6-pyridino moiety are described.

2-Bromo-6-lithiopyridine, generated from 2,6-dibromopyridine and *n*-butyllithium, was used to synthesize 2,6-*bis*[2′-(6′-bromo-picolinoyl)]pyridine and *bis*-2-(6-bromopyridyl)ketone in 36% and 63% yield, respectively. Ketalization of these ketones was accomplished by either standard acidic or basic conditions.

To model a nucleophilic substitution route for cyclization of the resulting ketals, lithioacetonitriles were allowed to react with bromopyridines to produce symmetrical and unsymmetrical cyanomethine adducts in more than 47% yield. Reaction of 2,6-*bis*-[2′-(6′-bromopyridyl)-1,3-dioxolan-2-yl]pyridine or 2,2-*bis*-2′-(6′-bromopyridyl)-1,3-dioxolane with lithioacetonitrile afforded $[1_n]$(2,6)pyridinophanes (n=3,4), in which the pyridine rings were coupled with ketal and cyanomethine functionalities. At 80°C, cyclocondensation via nucleophilic substitution favors macrocycle formation because the intermediates are held in the desired *syn*-conformation by a metal ion template effect.

The ketal and nitrile groups of the initially generated macrocycles were hydrolyzed under acidic conditions. Hydrolysis of

the nitrile was accompanied by decarboxylation to produce methylenic intermediates (**143** and **152**), which were oxidized with SeO_2 to afford the desired triketone **115** and tetraketone **125**, respectively. Alternatively, oxidation of the α,β-unsaturated nitrile tautomers with *m*-chloroperbenzoic acid to a keto group; followed by deketalization under acidic conditions afforded the same ketones.

Triketone **115** and tetraketone **125** contain only sp^2 carbon atoms and should be essentially planar; however, due predominantly to *N,N*-electron repulsions within the confines of the cavity, deformations from planarity were observed. The dihedral angles of pyridines in triketone **115** are 35.4, 41.4, and 46.5°, respectively.

Wittig reactions and the Knoevenagel condensations on the bridging carbonyl groups in triketone **115** were unsuccessful, but facile monohemiketalization of **115** was observed. X-ray analysis of a Cu(II) complex isolated from ethanol confirmed the presence of a hemiethyl ketal (**178**). Upon exposure to air, precursor **143** of triketone **115** underwent oxidization to afford dimeric $[1_3](2,6)$-pyridinophane, which was subsequently dehydrogenated with either 999DDQ or air. X-ray data of these dimers confirm the juxtaposition of the two electron-rich cores.

I. Artificial Enzymes

I-1. Introduction

Since Wöhler discovered his famous conversion of ammonium cyanate into urea in 1828, millions of organic molecules have been synthesized. Of these there are basically two general types: naturally-occurring compounds called natural products, and all the rest which do not exist in nature. The former are provided by the evolutionary chemistry[1] of nature; whereas, the synthetic targets for the latter are designed by the researcher. The selection of an appropriate target is however guided by numerous objectives, such as financial, synthetic challanges, to test its physical parameters or for sheer fun.

The study of enzymes has occupied a central place in the physical biological sciences for many years, and the catalytic prowess of these naturally-occurring substances has long fascinated chemists. Substrate binding to an enzyme or receptor, assembling of protein complexes, intermolecular reading of genetic codes, signal induction by neurotransmitters, and cellular recognition are but a few important characteristics of enzymes. Either substrate/enzyme or inhibitor/receptor complexation can be a key feature in catalysis and regulation of biological processes. Cooperation between catalyzing functional groups in enzymes is possible only if those sites are held in positions that converge on a substrate-

binding locus, usually located in a cavity. Thus, the design, synthesis, and study of cavity-containing organic molecules are the principal themes in what is termed host-guest[2] or ("receptor-substrate")[3] chemistry.

Many investigators have long dreamed of commercially available synthetic catalysts that would imitate the desirable properties of enzymes. Only within the last decade, however, have serious attempts been made to mimic *in vivo* enzymatic action by means of simple synthetic models. Foremost amongst these models are the chemically modified cyclodextrins,[4] which contain rigid cavities derived from the cyclic oligomers of 1,4-glucopyranoside. Their rigid, torus-shaped cavities, which are derived from either six (α-cyclodextrin), seven (β-cyclodextrin), or eight (γ-cyclodextrin) saccarides (see Fig. 1), are large enough to embrace even an aryl moiety. Among the interesting enzyme modeling reactions, cyclodextrin glycosyl transferases, a type of amylose, can detach a turn from the starch helix and link the two ends of this fragment to give a cyclic molecule.[5] These cyclodextrins also have

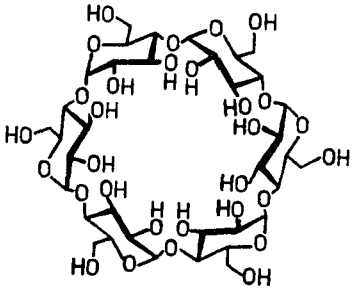


Fig. 1. α-Cyclodextrin

disadvantages;[6] in that they are biodegradable and only a limited array of cavity sizes can be isolated from starch fermentation by *Bacillus macerans*.

Therefore of great interest to the chemist is the total synthesis of many molecules, which possess structures similar to the cyclodextrins but are amenable to greater structural variation and control. Other important cavities in the biological world include the binding sites of enzymes and the troughs in RNA and DNA helices; however, progress in duplicating the reactivity of these highly stereospecific catalysts has been initiated but still rather limited.

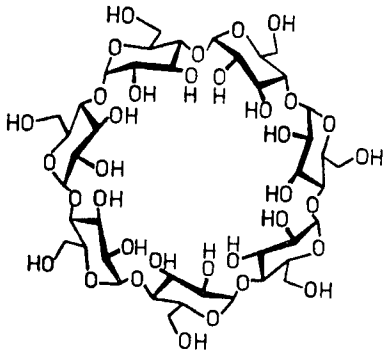
I-2. The Host-Guest Chemistry

Highly structured molecular complexes[2a] are composed of at least one host molecule and one guest molecule, each possessing a complementary stereoelectronic arrangement of binding sites and steric barriers. Hosts, the synthetic counterparts of biological receptors, are conveniently defined as organic compounds containing convergently arranged binding sites. Molecular hosts are usually larger than their guests since positioning of convergent binding loci involves a support framework not required for guests. Guests, the synthetic counterparts of substrates, possess divergently arranged binding sites and may be either neutral or ionic (in)organics, or metal ions.

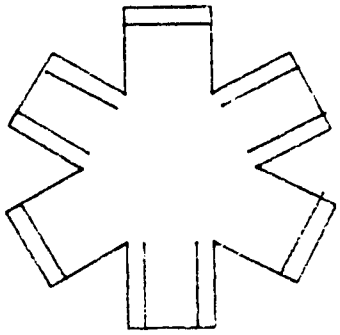
Host-guest complexes are formed when the molecular shapes and binding sites of the host(s) and guest are complementary. A complex is composed of a host and guest held in a definite structural relationship. The forces attracting binding partners[1b] include, but are not limited to: hydrogen bonding, ion-pairing, ion-dipole, pi-acid to pi-base, van der Waals forces, and solvent liberation phenomena (in water solution, hydrophobic binding). These forces are generally weak when compared to the strength of covalent bonds, so multiple contacts within a given binding site are needed to create stable complexes.

If organic solvents are employed for reactions with crown ethers and cryptands, the major driving forces[7] for complexation are most notably charge-dipole interaction and/or hydrogen bonding. Reaction with cyclodextrins and cyclic polyions are, however, usually conducted in water; thus the major driving forces for complexation are hydrophobic and charge-charge interactions, respectively. Crown ethers, cryptands, and cyclic polyions are completely synthetic hosts; whereas, cyclodextrins are "*semi*-synthetic hosts" in that some chemical modifications[5] are still possible.

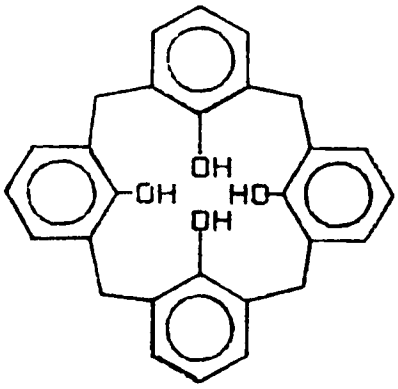
Because the first step in enzymatic reactions is host-guest complex formation (e.g. enzyme and substrate), the initial problem facing the organic chemist is undoubtedly the design and synthesis of artificial hosts having specific cavities of definite structure to accommodate the particular guest. Several groups of artificial hosts[7] have been developed so far: (a) modified cycloamyloses



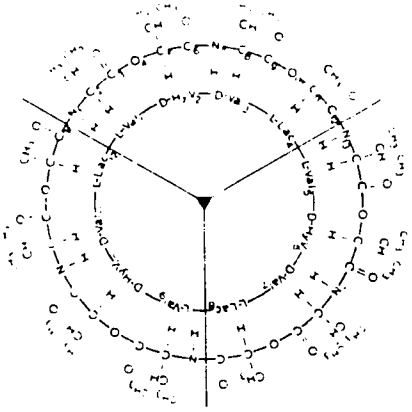
(a) β-Cyclodextrin
(Cycloamylose)



(b) [18]annulene
(Cycloalkene)

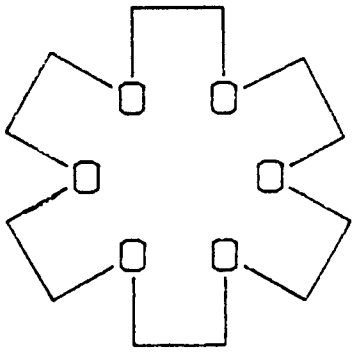


(c) Calix[4]arene
(Cyclophane)

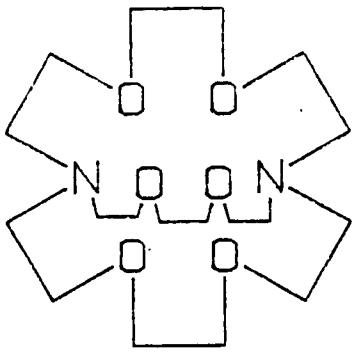


(d) Valinomycin
(Cyclic Peptide)

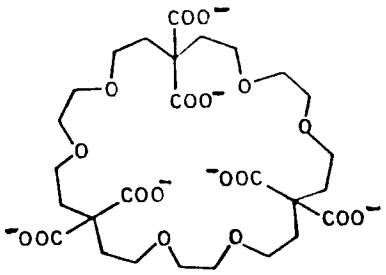
Fig. 2. Examples of Artificial Hosts.



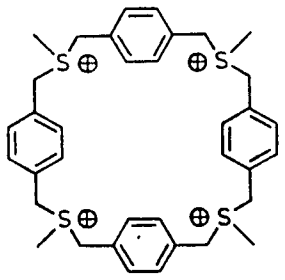
(e) [18]crown-6
(Crown Ether)



(e') [2.2.2]cryptand
(Cryptand)



(f) Macrocyclic Hexa-
carboxylic Acid
(Cyclic Polyanion)



(f') *S,S',S",S"'*-Tetramethyl-
2,11,20,29-tetrasulfonium
[3_4]paracyclophane
(Cyclic Polycation)

Fig. 2. (Cont'd.)

(cyclodextrins),[4] (b) cycloalkanes,[8] (c) cyclophanes,[9] (d) cyclic peptides,[10] (e) cyclic neutral polyligands such as: crown ethers,[11] cryptands,[3,12] and (f) cyclic polyanions[13] and cations.[14] All of these are macrocycles and are intrinsically suitable as artificial hosts because they generally contain stable and well-defined inclusion cavities. Of these macrocyclic hosts, the cyclodextrins, crown ethers, cryptands, and more recently cyclic polyions have been widely and systematically studied.

Although clathrates[11] and cyclodextrins have been the subjects of active research for many decades, there is little doubt that the arrival in 1967 of the "crown ethers", as readily available hosts, provided the timely stimulus for the rapid development of supramolecular chemistry. Immediately following Pederson's accidental discovery[16] of crown ethers, significant early contributions were made by Lehn[3,14b] and Cram.[1a] It was apparent that a new branch of chemistry, which straddles many scientific disciplines, was beginning to emerge.

Although for many decades cyclophanes have been the subjects of active research, the rediscovery in 1980 of the so-called "calixarenes" as readily available synthetic molecular receptors, increased development of supramolecular chemistry. Another unique class of potential hosts, heterocyclophanes, i.e. molecules containing at least one heterocyclic ring as part of the cyclophane structure, has been under development. This dissertation will, thus, be limited in scope to the synthetic aspects leading to *carbon-bridged* cyclophanes and heterocyclophanes ("heterophanes"),

including the π-excessive[17] heterocycles (pyrrole, furan, thiophene, and related five-membered rings) and the π-deficient heterocycles (pyridine). In addition, mixed heterophanes, which may contain both π-excessive and π-deficient aromatic moieties are herein considered.

For convenience, a macrocycle will be defined as a 11- or larger membered ring; several smaller membered rings have been included in order to define the lower limits of construction. Macrocycles of biological origin were not included, unless synthesized from or degraded to smaller, important fragments. Porphyrins and related macromolecules have also been omitted; however, several simple pyrrole macrocycles have been included for comparative purposes.

I-3. Nomenclature

Numerous nomenclature and numbering rules have been proposed and adapted for easy identification of the organic structures. In general, as the IUPAC notation[18] for 1 illustrates, application of this systematic nomenclature system to macrocycles herein under consideration is too cumbersome for routine, general scientific use. For heterocyclophanes, especially if they are polyfunctionalized, the systematic names become increasingly complicated; thus, virtually no authors in the field use the IUPAC notation for these macromolecules. In order to partially circumvent this problem, "phane nomenclature"[19] has been used in this dissertation. For

example in IUPAC nomenclature, a specific cyclophane (represented by **1**) is named and numbered as shown in Fig. 3. An alternative nomenclature for this type of ring structure was suggested by Cram and Steinberg[20], in which **1** was named [1•1•1•1]- or [1_4]-metacyclophane. Several research groups[21] have reported the syntheses of the tetrahydroxy derivatives of **1** (i.e. **2** in Fig. 4) and have named them in various ways, e.g., "cyclischen Mehrkermethylenephenolverbindungen",[21] "cyclictetranuclear novolaks",[22] and "tetrahydrocyclotetra-*m*-benzylenes."[23] For convenience, Gutsche et al.[24] have chosen to call them "calixarenes" (Greek, *calix*, chalice; *arene*, including the incorporation of aromatic rings in the macrocyclic array), specifying the size of the macrocycle by a bracketed number inserted between *calix* and *arene* and specifying the nature and position of substitution on the aromatic rings by appropriate numbers and descriptors.

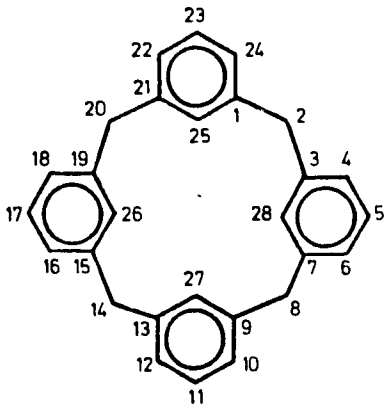


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Fig. 3. Pentacyclo[19•3•1•$1^{3,7}$•$1^{9,13}$•$1^{15,19}$]octacosa-1(25),3,5,-7(28),9,11,13(27),15,17,19(26),21,23-dodecaene.

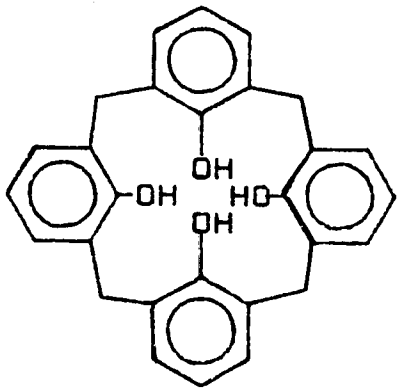

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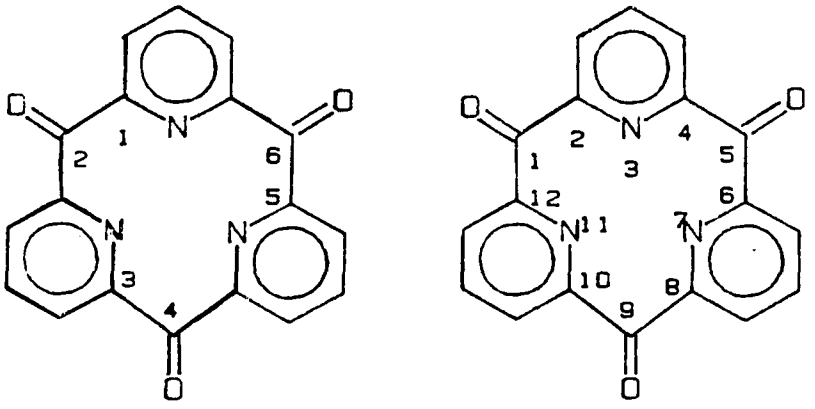
Fig. 4. Calix[4]arene

However, since a drawn structure can not be misinterpreted, this dissertation will approach the communication problem by inclusion of the parent structure and will indicate the site(s) of substitution by adopting a modified numbering scheme proposed by Gol'dfarb et al.[25] as well others.[26] (see Fig. 5) The "Phane" system of nomenclature proposed by Vögtle and Neumann[19] has herein been utilized only when a formal identification of a macrocycle was necessary.

In order to circumvent the disadvantage of the "Phane" system, Weber and Vögtle suggested "coronand" nomenclature.[2b,27] Accordingly, a distinction was made between the classical cyclic oligoethers ("crown ethers") and monocyclic coronands. The multidentate monocyclic ligands with any donor type were called "coronands", while the term "crown ether" is reserved for cyclic oligoethers containing *exclusively* oxygen donors. For example, Figure 5 shows the "Phane" and "coronand" names for 19,20,21-triazatetracyclo[13·3·1·$1^{3,7}$·$1^{9,13}$]heneicosa-1(19),3,5,7(21),9,11,-

13(20),15,17-nonane-2,8,14-trione in IUPAC nomenclature. Other than this brief introduction and the example cited below, these systems of nomenclature will not be considered further but in the forthcoming pages the least complicated name will be used.

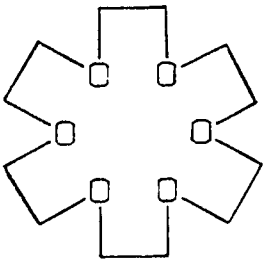


"Phane" numbering "Coronand" numbering

Fig. 5. 'Phane': 1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione.
'Coronand': 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione.

Another nomenclature was proposed[2b,12,28] in which, in place of the clumsy IUPAC name 1,4,7,10,13,16-hexaoxacyclooctadecane, cyclic polyether **3** becomes [18]crown-6 and **4** becomes dibenzo[18]-crown-6. The specific classification crown is preceded by the total ring size in sequare brackets and succeeded by the number of heteroatoms in the ring. The dibenzo refers to the two benzene rings fused onto the ring. The other trivial nomenclature was

introduced[2b,12,28] for the diaza cryptands in which the number of oxygen atoms in each chain in square brackets precedes the specific classification, cryptand. Thus, cryptand **5** is named [2.2.2]-cryptand and its derivative with only one oxygen in one of the chains would be [2.2.1]cryptand. Although more specific and illustrative the new nomenclature suffers in more complex cases from name lengths comparable to those of the IUPAC system.



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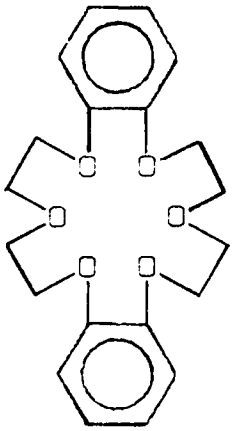

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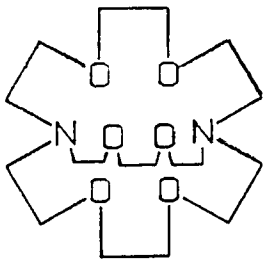

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II. Cyclophanes

II-1. Introduction

Although the relationship between the concept of cyclophanes, a product of the imagination of the synthetic organic chemist, and biological processes may seem rather remote, cyclophanes are well worth consideration by chemists who wish to design and prepare synthetic analogs of enzymes and receptors. Completely artificial cyclophane-type hosts have several advantages: a) straightforward preparation, b) well-defined molecular dimension, size or shape (determined from X-ray crystallographic study), c) easily obtained information on various physicochemical properties, such as macroring conformation and internal rotation of aromatic rings, and d) remarkable thermal and/or chemical stability.[29] Moreover, the structural variability of cyclophanes makes it easy to prepare modified macrocycles for very specific interactions with certain guests.

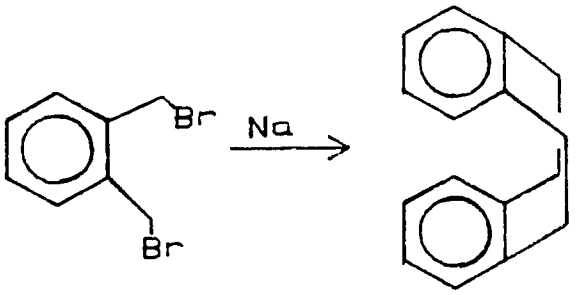
For an introduction to the interrelationship between (hetero)cyclophanes, this Chapter will deal with the synthesis of carbon-bridged cyclophanes. Chapter II-3 details the syntheses of calixarenes, which are pseudoisosters of porphyrinogens (see Chap. III-3) with phenol derivatives. Many physical properties[24] of calixarenes are similar to those of heterocyclophanes.

II-2. Syntheses of Cyclophanes

There has been considerable interest[1] in comparing the properties of different [N_m]cyclophanes (N=1,2,3; m=1,2,3,4) since these are affected by differing bridge members and patterns. Historically, the syntheses of [n]paracyclophanes[30] have been approached through reactions commonly used for the preparation of medium- and large-ring (hetero)arylcycles. Several traditional methods described by Smith[31] are: acyloin condensation, Friedel-Crafts reaction, pyrolysis of diacids, cyclization *via* amide formation, halo-amine cyclization, halo-ether cyclization, Ziegler cyclization, and oxidative coupling of acetylenes and mercaptans. In 1964 when *Bridged Aromatic Compounds* was written,[31] [8]paracyclophane was the smallest [n]paracyclophane yet described, although Allinger and coworkers[32] had speculated that [7]paracyclophane would be about as strained as cyclopropane and therefore amenable to synthesis. Syntheses of these highly strained targets prompted a search for new preparative procedures. In the synthesis of [N_m]cyclophanes, numerous general synthetic methods[33] have been found:

A. The Wurtz coupling reaction is the oldest[33b] of synthetic methods to prepare cyclophanes, having been used by Baker et al.[34] in the original synthesis of [2_2](1,2)cyclophane (6), and later employed by Cram and Steinberg[20] for the preparation of [2_2](1,4)cyclophane (7). Although, in general, yields observed in

the Wurtz coupling are usually low (ca. 20%), it is a useful method when the required dihalide is readily available.



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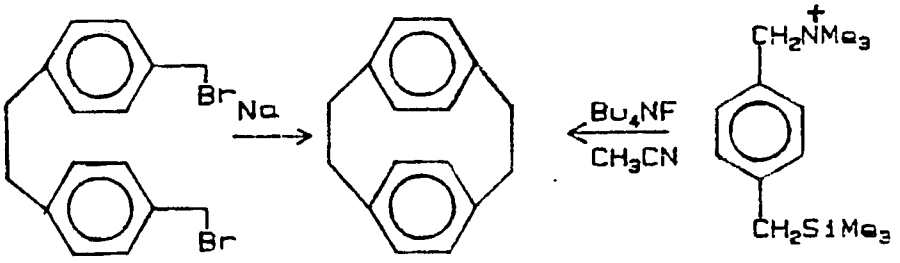

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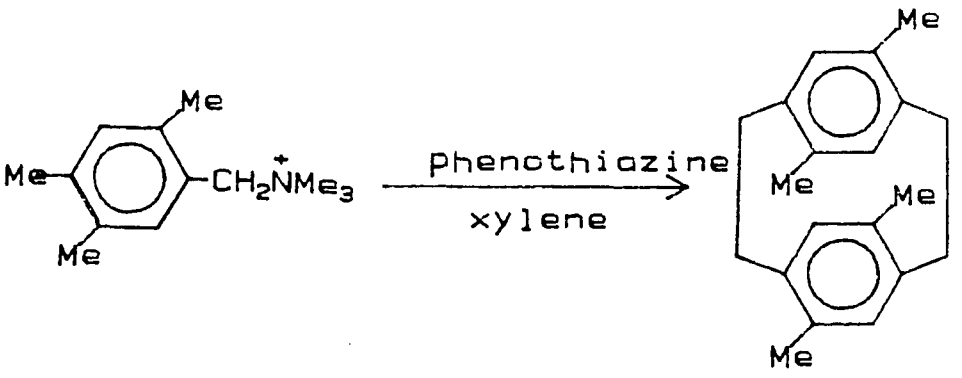
B. The Hofmann-type, 1,6-elimination of *p*-methylbenzylammonium hydroxides[35] has been used to synthesize various of $[2_2](1,4)$cyclophanes and particularly valuable for preparing multilayered cyclophanes.[33b] Although yields in these 1,6-eliminations as shown for the preparation of 8 are usually low, Otsubo et al.[36] have shown that improved yields (27%) can be obtained by careful attention to solvent, concentration, and inhibitor. Recently, Ito et al.[37] reported the synthesis of 7 in 56% yield by an interesting variation involving fluoride ion attack on the trimethylsilyl analog (9).



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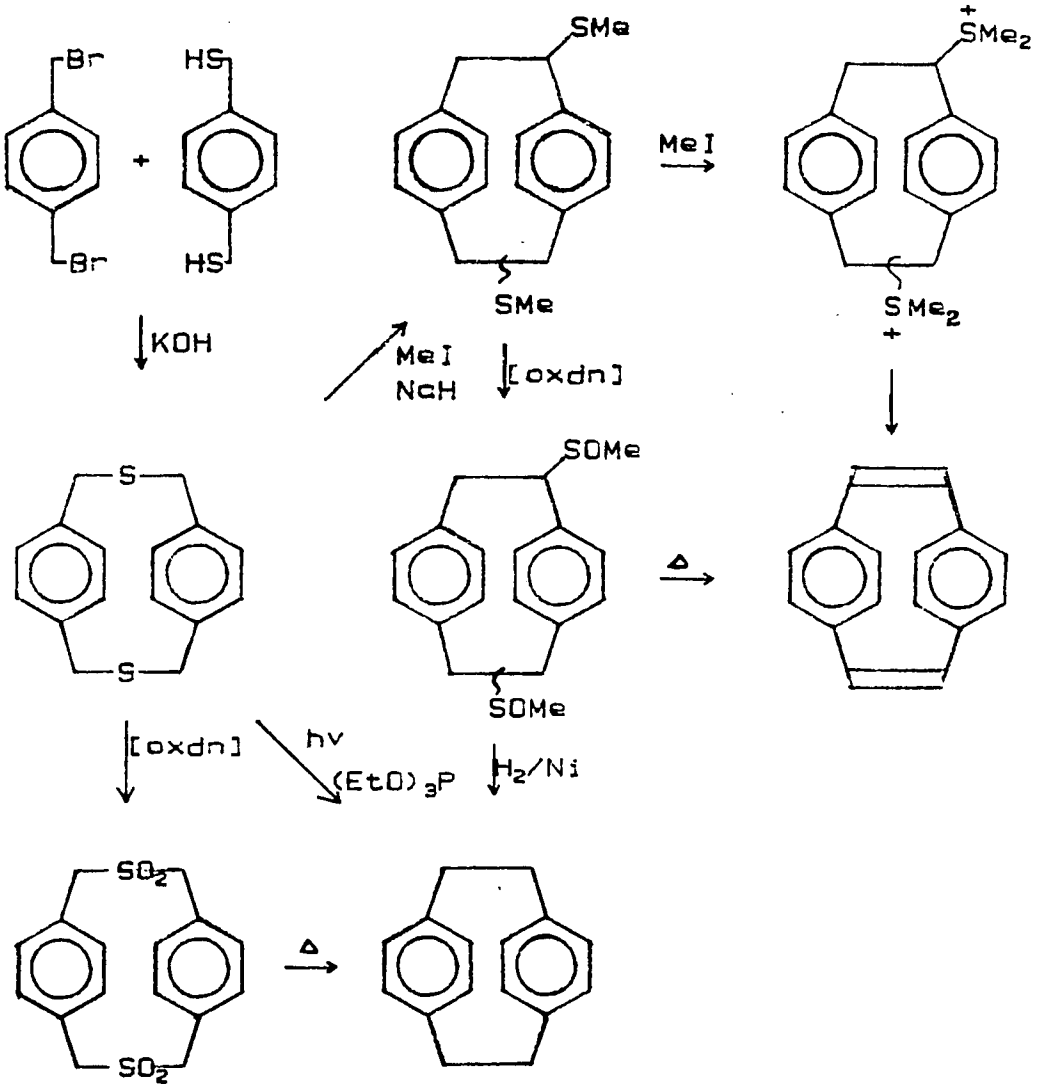
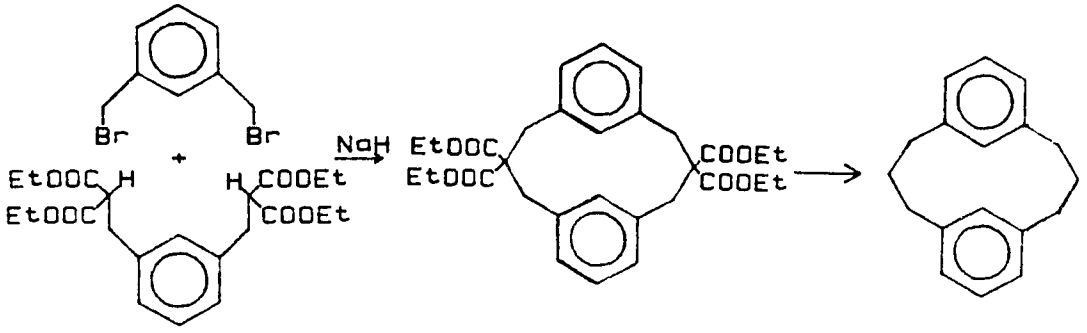
C. Ring-contraction *via* *S*-Extrusion of thiophanes (*S*-bridged cyclophanes) has been used to generate [2.2]cyclophanes. These thiophanes are readily available in relatively high yields by ring-closures using high-dilution principles[33a] and are the cyclic precursors of the corresponding *C*-bridged cyclophane. The intermediates are very stable and easy to handle, and the pyrolysis could be treated at 500-600°C. Yields of the corresponding cyclophanes as high as 80% could be achieved. Sulfide ions generated from either $Na_2S \cdot 9H_2O$ or thioacetamide have been used for the successful preparation of thiocycloalkanes, crown ether sulfides, and thiophanes. The contraction can be achieved by various *S*-extrusion procedures, such as: a Stevens rearrangement,[38] photoreaction of the thioether in the presence of phosphorus compounds,[39] and pyrolysis of the corresponding sulfone,[40] which is easily obtained by facile *S*-oxidation.



D. A Malonate Approach to generate cyclophanes is an important but little used method for the synthesis of [3•3]cyclophanes. *Meta*-xylene-α,α-diethyl malonate (10) and 1,3-bis(bromomethyl)-benzene were condensed in boiling xylene with excess NaH to give [3•3]cyclophane-tetraester 11. The formation of saturated

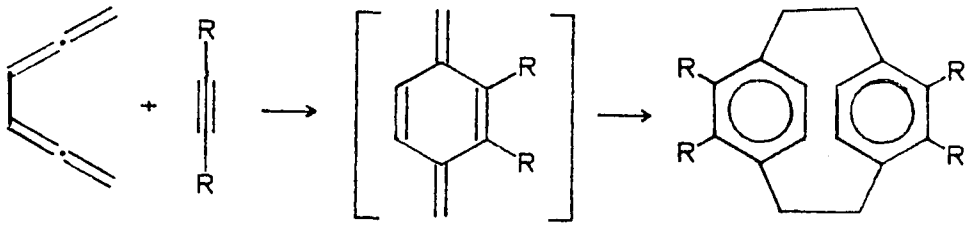
[3•3](1,3)cyclophane from tetraester **11** proceeded *via* three steps: a) hydrolysis and decarboxylation (86%) under acidic conditions, b) α-substitution (75%) with chloride under $Pb(OAc)_4$/LiCl/pyridine, and c) reduction (61%) of chloride with Li/*t*-BuOH.[40] However, the strong bases required to produce the bis-malonate anions limits this classical direct *C-C*-coupling method to educts and products that are insensitive to bases. Today, cyclophanes, such as [3•3]cyclophanes, can be prepared more directly by the sulfur extrusion from [4•4]thiophanes by pyrolysis or photolysis.



10 **11**

E. A Diels-Alder Reaction involving *p*-xylylene intermediates could be conducted in concentrated solution, giving as much as 60 grams per run.[41] In 1972, Hopf[42] discovered that 1,2,4,5-hexatetraene (**12**) reacted with acetylenes **13** to give substituted [2•2](1,4)cyclophanes (**15**). Presumably the first step is a Diels-Alder reaction of **12** with **13** to give the *p*-xylylene (**14**), which subsequently dimerizes to generate **15**. In contrast to other cyclophane syntheses involving *p*-xylylene intermediates, this

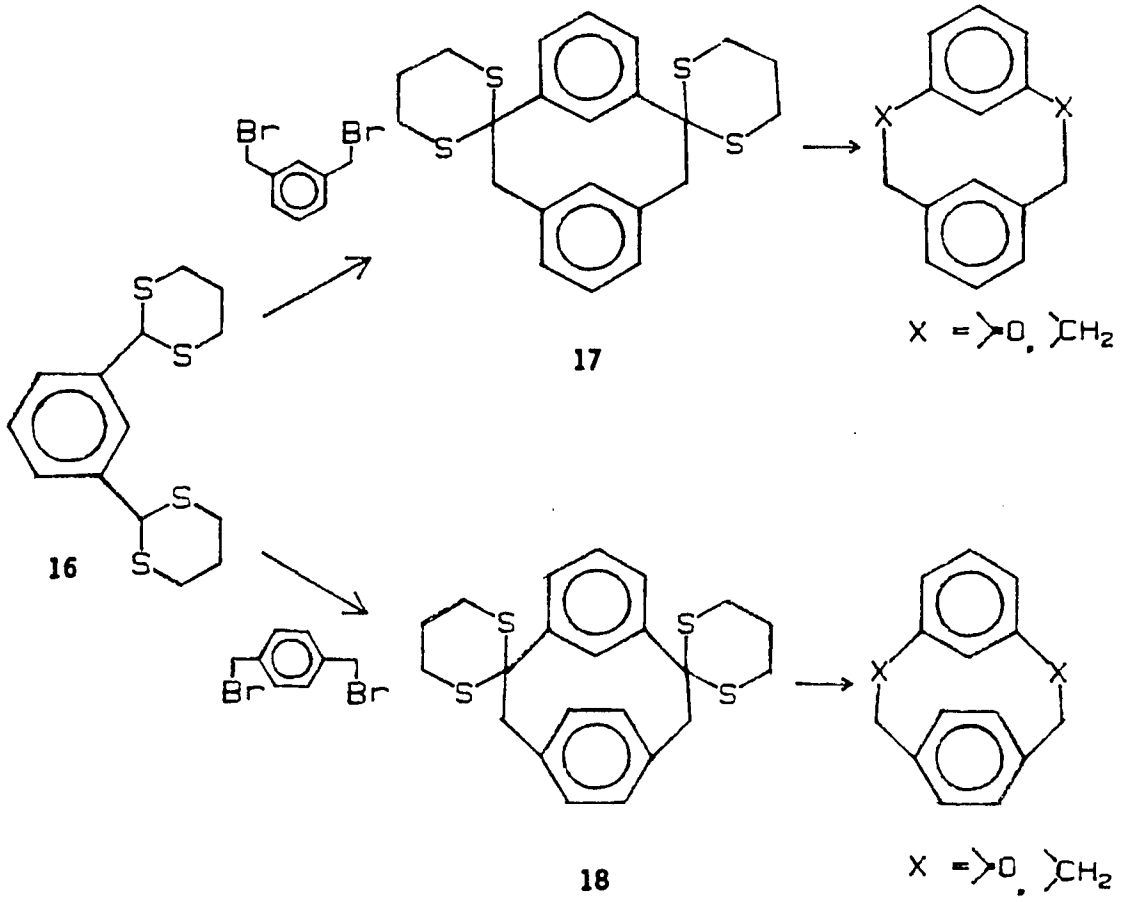
synthesis can be conducted in concentrated solutions affording (40-50%) the desired [2•2](1,4)cyclophanes.[41]



12 13 14 15

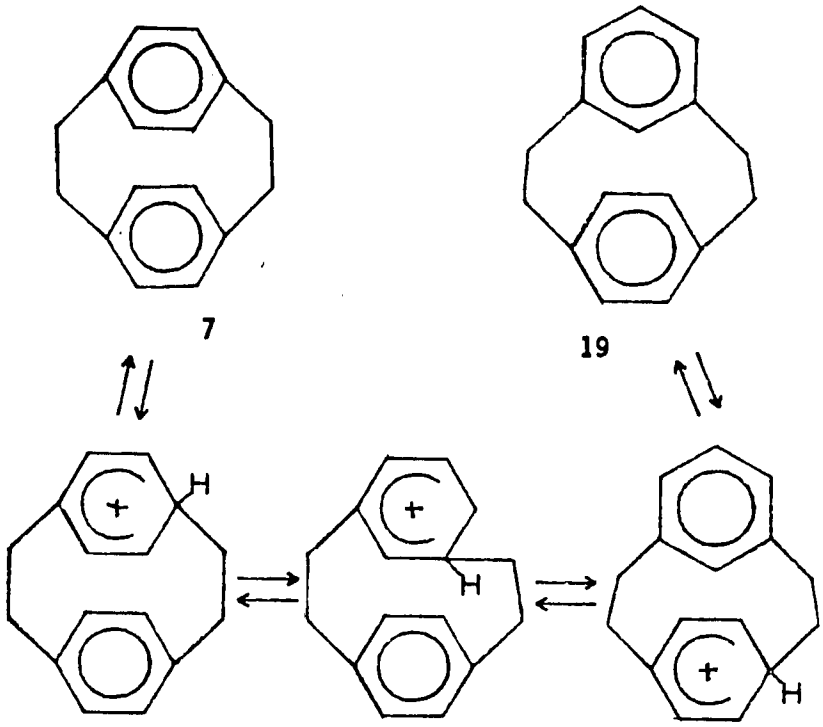
The Diels-Alder adducts of tetraene **12** and acetylenes **13** are very useful for preparing various methyl substituted [2•2]cyclophanes, in addition to acting as starting materials for multibridged cyclophanes.[33b]

F. The Bis(dithiane) Alkylation Method was introduced by Seebach et al.[43a] as a method for converting aldehydes to cyclic diketones. In an extension of this method, isophthalaldehyde bis(dithioacetal) (**16**) could be alkylated with either *m*- or *p*-xylylene dibromide to give the corresponding bridged-substituted cyclophanes (**17** or **18**, respectively).[43b-c] These, in turn, can be readily desulfurized with Raney nickel to provide the parent cyclophanes or hydrolyzed in the presence of mercuric chloride to give the corresponding cyclophane-1,9-diketones.

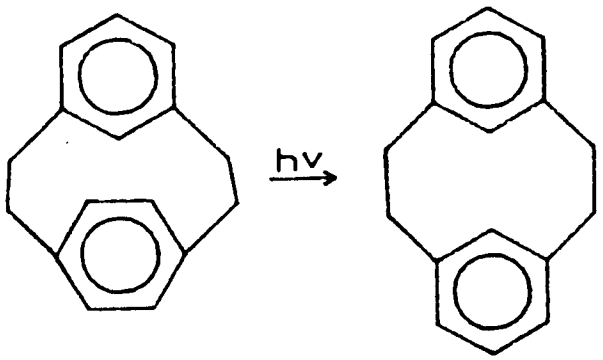


G. Cyclophane Rearrangements were observed by Cram et al.[44b,c] in their studies on the chemical properties of [2·2](1,4)cyclophane (**7**). Upon treatment of **7** with anhydrous hydrogen chloride and aluminum chloride in dichloromethane at -10°C, rearrangement occurred at give [2·2](1,3)(1,4)cyclophane (**19**). This rearrangement is intramolecular and probably follows a reaction path involving intermediates, such as **20-22**; the driving force for the rearrangement was thought to be the relief in strain in going from **20** to **22**, since **7** has ~8kcal/mol more strain energy than **19**.

Another possible driving force is the well-known fact that meta-dialkylated benzenes are stronger bases than para-dialkylated benzenes toward proton acids.



7 19 20 21 22



19 23

Accompanying their work on the Lewis-acid catalyzed rearrangement of **7** to **19**, Cram et al.[44d] observed that **19** underwent a photochemical rearrangement to give (46%) [2·2](1,3)cyclophane (**23**), which was inert toward prolonged irradiation.

II-3. Calixarenes

Calixarenes, which are [1$_n$]metacyclophanes, are macrocyclic phenol-formaldehyde condensation products similar in structure to certain cyclic polyethers, which were noted for their size-related selectivity in binding cations.[45] Calixarene have been suggested as potential enzyme mimics because they possess a torus-like architecture similar to that of cyclodextrins.

The calixarenes were first reported by Baeyer[46] in 1872, when aqueous formaldehyde and phenol were heated to give a hard, resinous, noncrystalline product. The techniques at that time, however, were not adequate to allow characterization of such materials and thus the structure remained unknown. Three decades later, Baekeland devised a process for using this phenol-formaldehyde procedure to make a tough, resilient resin (called "phenoplast"), which was marketed with tremendous chemical success under the name "Bakelite". As a result, considerable industrial and academic attention was focused on this "phenol-formaldehyde process", and significant literature arose dealing with phenoplasts.[47] Among these investigations were those conducted by Zinke et al.[48] in connection with the "curing" phase of the process

in which various *p*-substituted phenols with aqueous formaldehyde and sodium hydroxide were heated at 200°C to afford very high-melting, highly insoluble materials, all of which were postulated to be cyclic tetramers, i.e. calix[4]arene. However, no experimental evidence supporting this postulate was cited.[45] More recently, by applying dynamic NMR spectroscopy as well as other modern techniques, Gutsche et al.[24,49] demonstrated that condensation of *p-tert*-butylphenol and formaldehyde gave *p-tert*-butyl-calix[4]arene, -calix[6]arene, and -calix[8]arene.

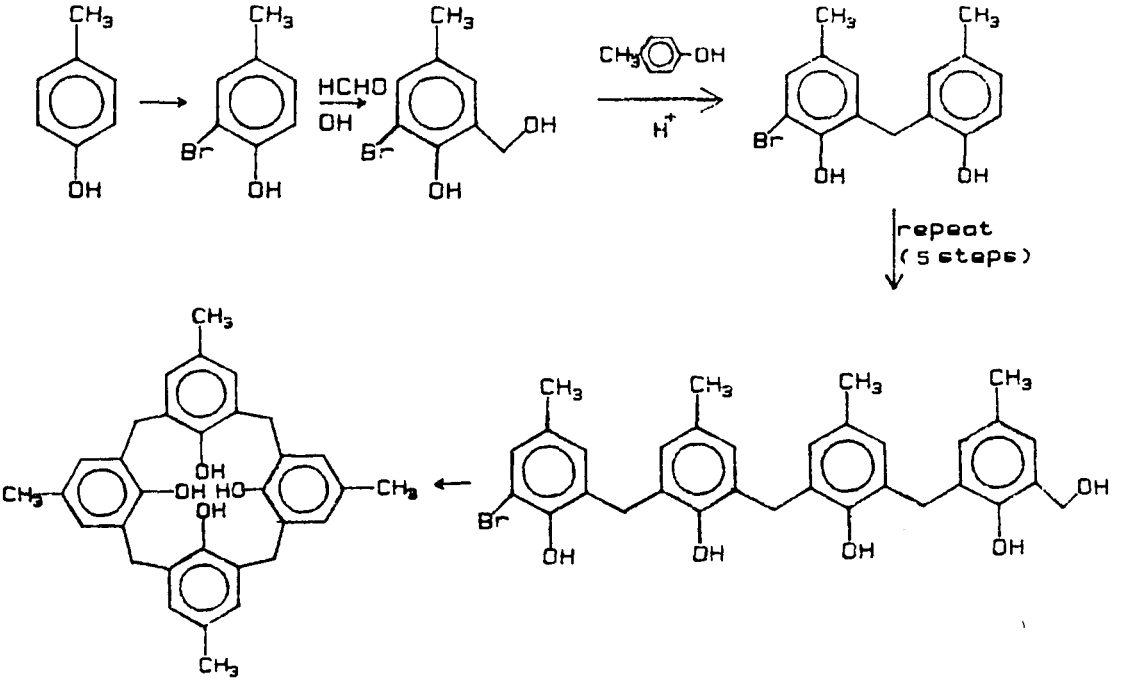
Calixarenes have been synthesized by two fundamentally different methods. The first was the lengthy multistep process devised by Hayes and Hunter,[50] in which (Scheme 1), *p*-cresol was protected at one of the *o*-positions by bromination, then the methylene groups were added by hydroxymethylation with formaldehyde. The aryl groups were appended by acid-catalyzed arylation, then the linear *o-bromo-o'-hydroxy-methyl* tetramer was debrominated and cyclized. The overall yields[45] of each of these materials is under 0.5%, making this a less than ideal procedure. The second method was recently reported[51] and exploited by Gutsche et al.[52] in which a simple, "one-flask" base-catalyzed condensation of a *p*-substituted phenol (24) with formaldehyde afforded a mixture of cyclic oligomers. Although the overall yields of 25 is only ca. 10%, the starting materials are inexpensive and the workup/purification procedure is generally simple and straightforward. If improvement in the selective hydroxymethylation could be realized,

the synthesis would excel the Zinke "one-flask" method not only with respect to flexibility, but also yield.

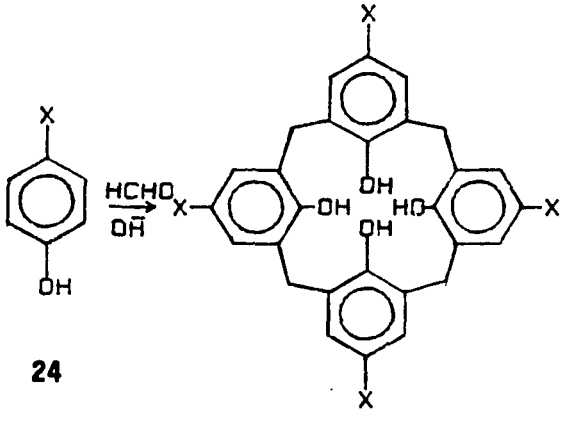
Calixarenes normally exist in the so-called "cone" conformation, in which all of the aromatic rings are oriented in the same direction, as shown by X-ray analysis[53] and dynamic ^{1}H NMR spectroscopy;[54] however, above 25°C they are flexible and undergo rapid interconversion between different conformations. The possibility of conformational isomerization in the calix[4]arenes was made by Conforth et al.,[23] who noted that four discrete forms can exist, and were labelled as "cone", "partial cone", "1,2-alternate", and "1,3-alternate" conformations by Gutsche et al.[55]

Two characteristics of the calixarenes are their unusually high melting points, invariably higher than those of their acyclic counterparts, and their low solubility in common organic solvents. the latter has frequently posed purification and characterization problems. The most interesting phenomenon with calixarenes, which have potential cavities, is their ability to complex suitable guests. *p-Tert*-butylcalix[4]arene (**25**, X=*t*-butyl) shows[56] a striking ability to form very stable complexes with numerous small molecules, including chloroform, benzene, and toluene. Only after prolonged heating at high temperatures and low pressures was it possible to completely expel these guests from these complexes. Evidence that the occluded guests are *inside* the calixarene was supported by an X-ray crystallographic determination[53] of the toluene complex of **25** (X=*t*-butyl), which clearly showed that the

Scheme 1. Ten-Step Synthesis of *p*-Methylcalix[4]arene



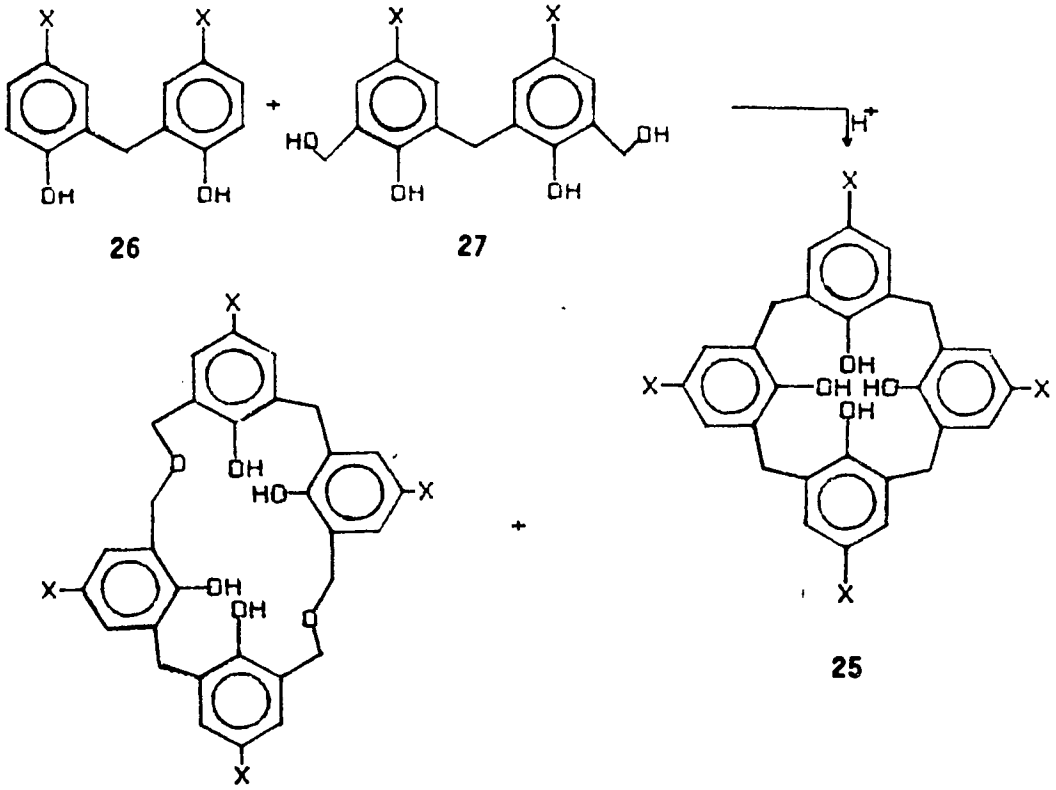
Scheme. 2. "One-Flask" Reaction for Calix[4]arene



24

25

toluene was *within* the host. *p-Tert*-butylcalix[4]arene, somewhat surprisingly, formed a very stable complex with one chloroform and two methanol molecules.[49] Upon heating at high temperature under vacuum, sequential loss of first one methanol molecule, then the second occurred, but the chloroform molecule was retained even after 144 hours at 257°C and 1 mm Hg.[49] Thus, an appealing feature of calixarenes is their ability to form very stable (irreversible) host-guest complexes by trapping neutral organics and small ions in their cavity.



26 27 28 25

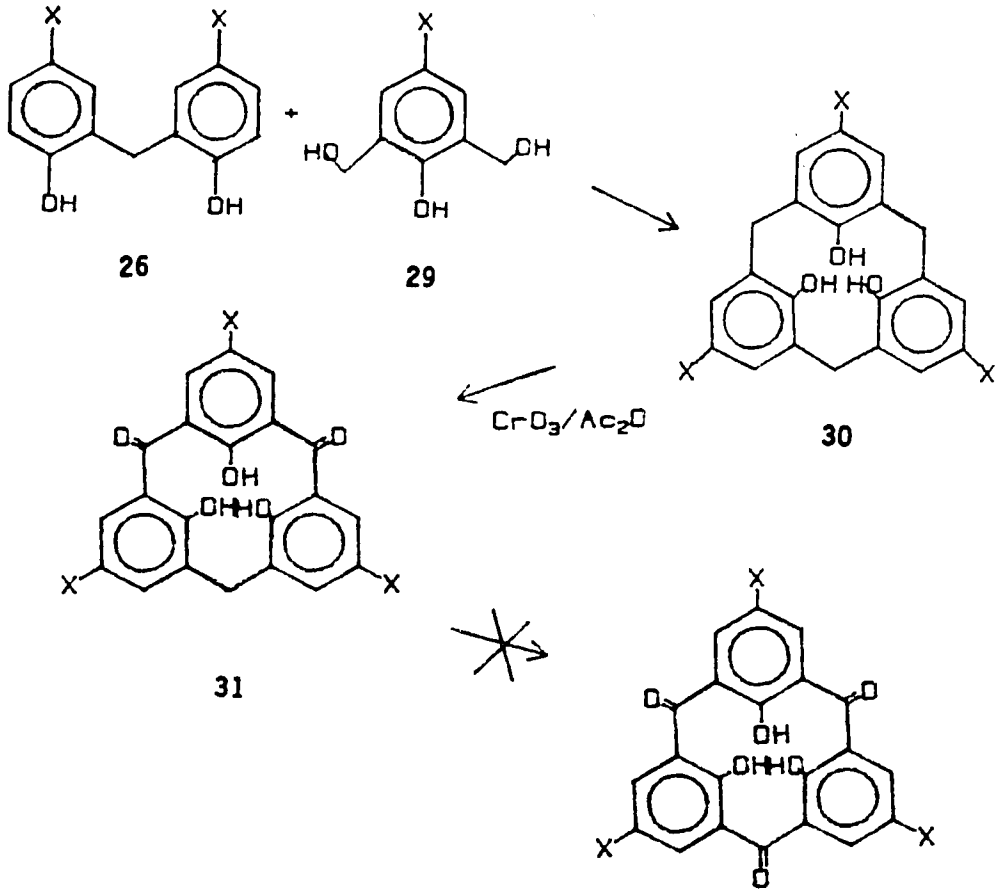
As part of an extensive program dealing with analogues of phloroglucides, Moshfegh et al.[57] have investigated the synthesis of various of *p*-halocalix[4]arenes using a procedure similar to that of Böhmer et al.[58] When **26** and the bis(hydroxymethyl) dimer **27** were used as starting materials, calixarene **25** was produced (65%) accompanied by 10% of ether **28**.

However, Böhmer reported quite low (best: 10-20%) yields in the cyclization step, in which a mixture of alkyl, bromo, and nitro functions were incorporated as X groups. This striking contrast in the yields between the methods of Böhmer and Moshfegh for the preparation of calix[4]arenes indicates that materials reported by Moshfegh et al. *might not be calixarenes*.

When Gutsche et al.[54b] recently synthesized *p*-halocalix[4]-arenes by an alternate procedure, high melting insoluble products were obtained. It is highly unlikely that the properties of the "Gutsche" compounds were significantly different from those prepared by Moshfegh,[57b] but were consistant with those observed for most calixarenes. Therefore, it must be conclude that the materials reported by Moshfegh et al.[57] were *not* calixarenes; definative structural data will unravel the mystery!

Even though Moshfegh et al.[59] reported the condensation of dimer **26** (X=Cl) with 4-halo-2,6-bis(hydroxymethyl)phenol (**29**) to afford (69-90%) *p*-halocalix[3]arenes (**30**) and the oxidation of the CH_2-bridges to give ketones **31**. The assigned structures (**30** and **31**) are considered doubtful at best.

Since space filling models of the calix[3]arene indicate considerably more non-bonded strain than in the higher-membered calixarenes, it is hoped that additional and more complete details in support of these structures will be forthcoming.

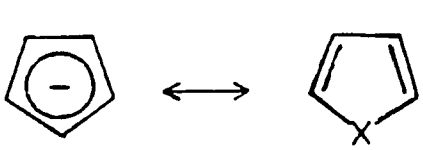


III. Heterophanes

III-1. Introduction

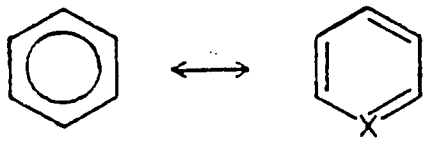
Heterocycles[17,60] are molecules which have a cyclic structure with two or more different kinds of atoms in the ring; however in most cases, carbon is still by far the most common ring atom.

Over the years, it has become clear that the chemical behavior of many heteroaromatics can be explained on the basis of two different types of aromatic ring systems: those derived from the cyclopentadienyl carbanion (32) by replacement of one or more CH groups by a heteroatom, such as: N, O or S, and those obtained by replacement of one or more CH group(s) (33) in benzene. These heterocycles can be regarded, to a greater of lesser degree, as aromatic on the basis of their physical properties and their resonance energies.



X = NH, O, S

32



X = N, P, As

33

Planar, unsaturated heterocycles containing five atoms can be considered as aromatic systems, if they have an uninterrupted cycle

of p-orbitals containing a total of six electrons. The carbocyclic analog of these heterocycles is the cyclopentadienyl anion, which is a planar, symmetrical pentagon with five sp^2-hybridized carbon atoms and a cyclic array of five p-orbitals containing the six electrons. Pyrrole, furan, and thiophene are examples of the five-membered aromatic heterocycles having six π-electrons distributed over these five atoms.

Nitrogen is the only atom from the first row of the Periodic Table which can replace a CH group of benzene and give an uncharged aromatic heterocycle. The orbitals of pyridine are qualitatively similar to those of benzene: they have the same symmetry and there are three bonding orbitals well separated in energy from three antibonding orbitals. However, the major difference is that the energies of the π-orbitals of pyridine are lower relative to those of benzene because of the greater electronegativity of the heteroatom. There is a shift of electron density from the ring carbons toward the heteroatoms; thus, these heteroaromatics are consequently classified as π-deficient.

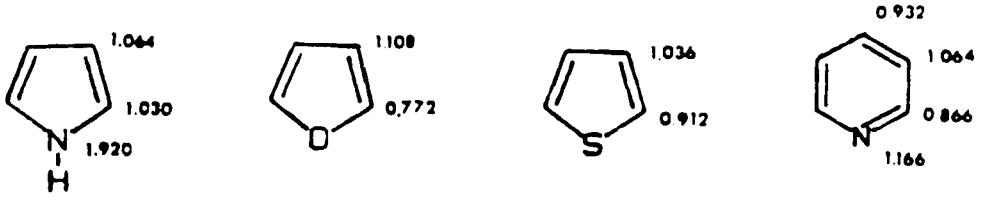
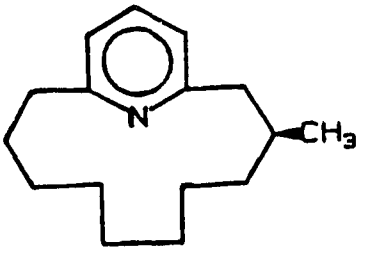


Fig. 6. Distribution of π-Electron Densities[17] in Pyrrole, Furan, Thiophene, and Pyridine.

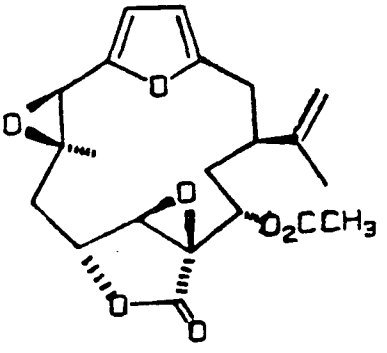
Based on theoretical and experimental information, some predictions[17,60] can be made with respect to the chemical reactivities of these heteroaromatics. For example, it is anticipated that, because of the decreased electron density on the carbon atoms of π-deficient systems, electrophilic substitution will be more difficult than in either π-neutral benzenoid or π-excessive heteroaromatic systems. Conversely, nucleophilic substitution in the π-deficient heteroaromatics is expected to be facilitated by the decreased electron density on the carbon atoms, in comparison to the π-neutral aromatics.

Heterophanes[61] are defined as cyclophanes with heterocyclic at least one subunit. Such molecules include π-excessive systems, for example, furano, pyrrolo, thiopheno, and related five-membered ring, and π-deficient systems, such as pyridino and pyridazino.

There are numerous compounds of biological origin and with biochemical significance that may be considered heterophanes, such as muscopyridine,[62] isolated from the perfume gland of the musk deer, and sea whip neuromuscular toxin Lophotoxin[63] with a functionality and a multiple ring structure that make it unusual among marine natural products.



Muscopyridine



Lophotoxin

In recent years, there has been increased interest in the chemical and physical properties of porphyrins and related macrocycles. This interest has been stimulated in part by the desire to understand the behavior of their metal complexes in biological processes. Chlorophyll and vitamin ("vita amine") B_{12} are but a couple of examples of naturally occurring compounds related to porphyrins.

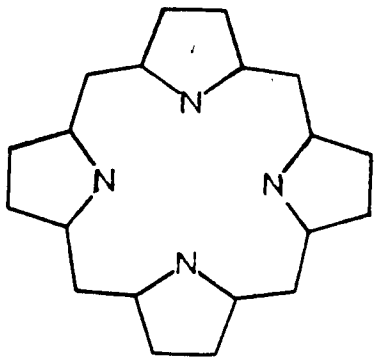
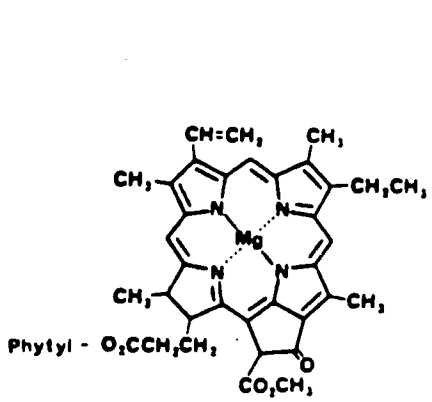
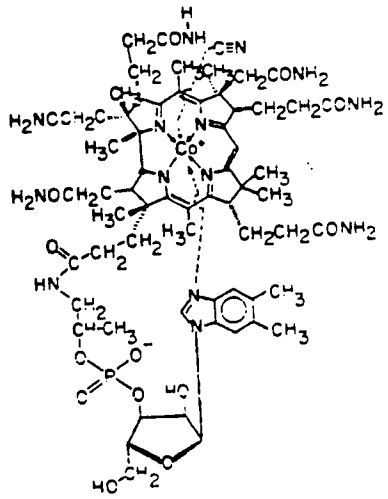


Fig. 7. Porphyrin Skeleton



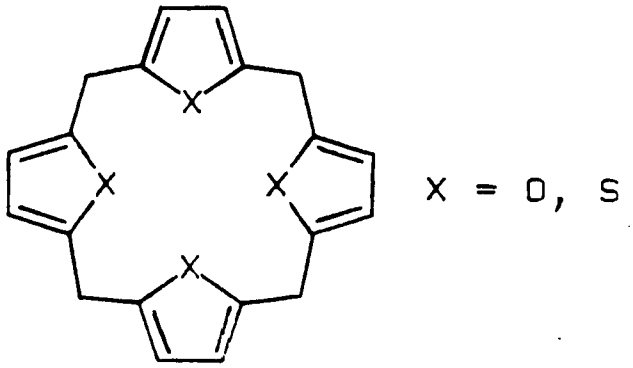
Chlorophyll a



Vitamin B_{12}

Fig. 8. Related Compounds to Porphyrins

Pyrrole of the porphyrinogen system[64] can be substituted by other heterocycles to give the isosters **34**.[61] These macrocycles are also of intrinsic chemical interest because of their relationship to the aromatic [18]-annulenes.



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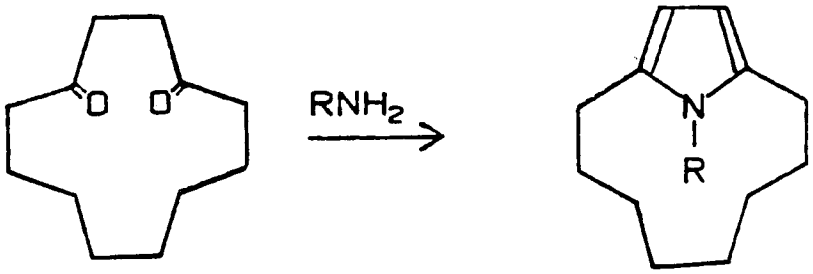
III-2. (2,5)Pyrrolophanes and Porphyrins

For the synthesis of simple (2,5)pyrrolophanes having alkane bridges with methylene groups, adaptation of the Paar-Knorr synthesis[65] provides a general convenient route to the [N](2,5)-pyrrolophanes (**35**, N=8[66] from cyclodecane-1,4-dione).



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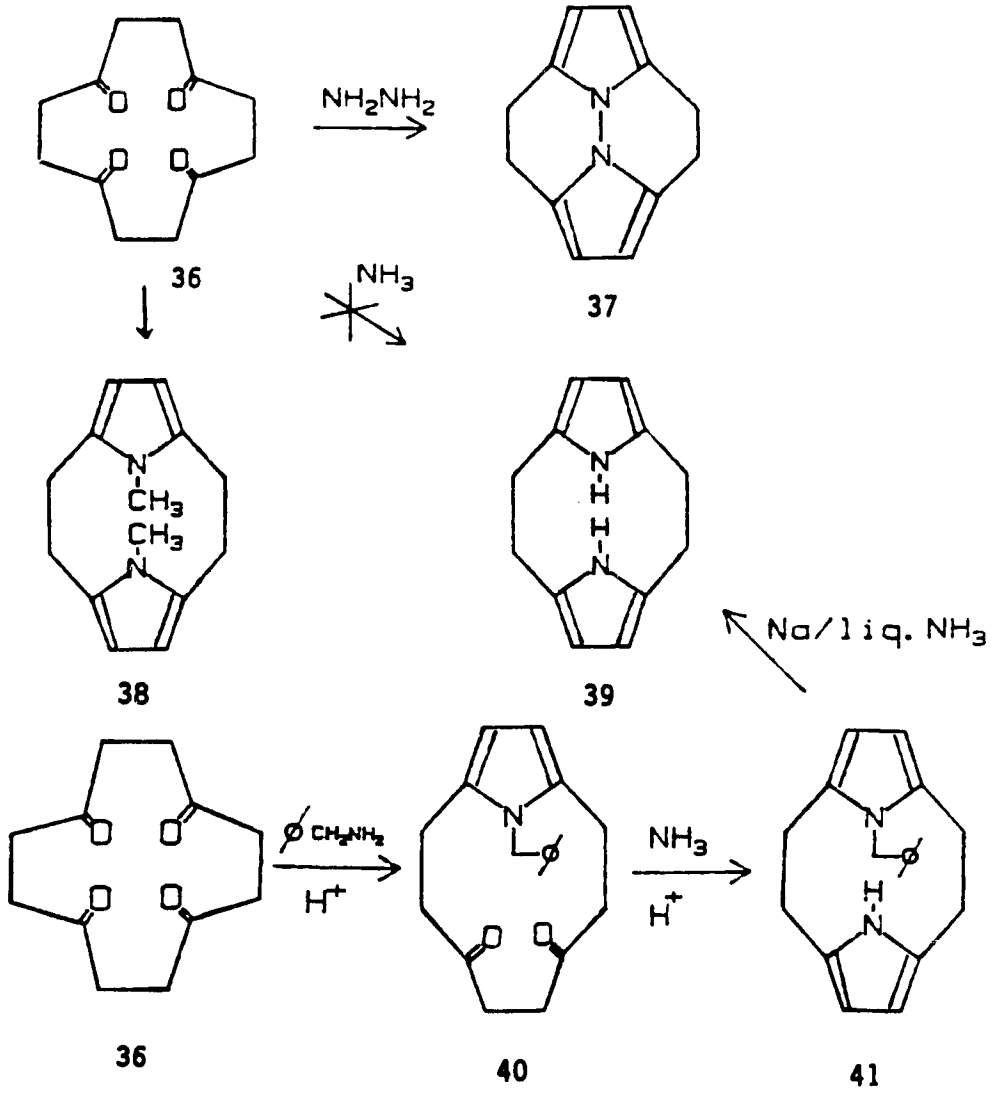
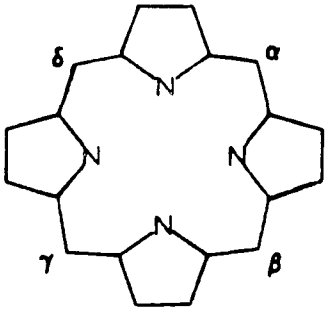
The Paar-Knorr procedure, utilizing cyclic 1,4-diketones, was extended to the synthesis of several mixed [2•2](2,5)pyrrolophanes.[67] Thus, reaction of cyclododecane-1,4,7,10-tetraone **36** with hydrazine and primary amines gave the symmetrical [2•2](2,5)-pyrrolophanes (**37**, not a phane) and **38**, respectively. The reaction of **36** with ammonia failed to give the *N*-unsaturated [2•2](2,5)-pyrrolophane (**39**), which however was obtained[68] via the reductive cleavage the *N*-benzyl derivative **41**,



obtained in good yield from the sequential reaction of **36** with benzylamine and ammonia.

Porphyrins are a class of tetrapyrrole macrocycles with a skeleton as shown in **42**. The porphine (the parent compound) free base **43** has 11 double bonds and can be transformed into a metalloporphine **44** by replacement of the two inner protons by a divalent metal ion. One can also add two additional protons to the free base and obtain the porphyrin dication **45**. Protoporphyrin IX (43) is one of the most abundant naturally occurring porphyrins. These three compounds related to the porphyrin nucleus are especially important to the overall chemical role played by the porphyrins. Replacement of the α,β,γ, and δ carbons by nitrogen and fusion of a benzene ring on the pyrroles afford the well-known dye, phthalocyanine **46**.[69]



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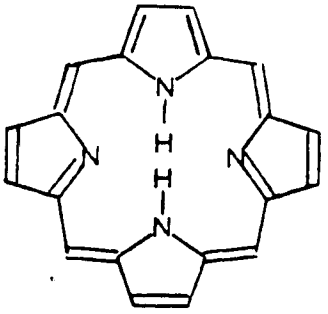

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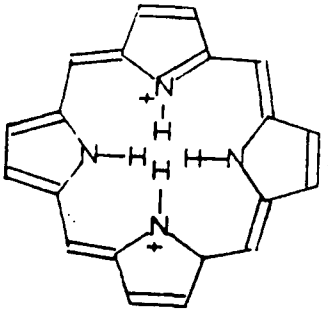

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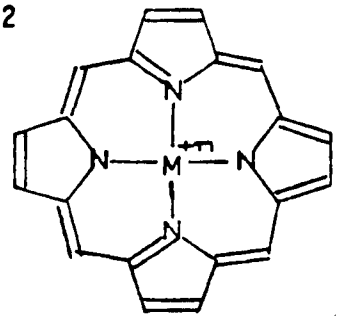

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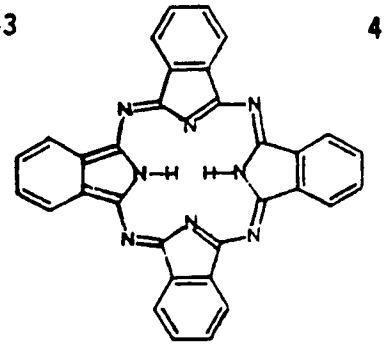
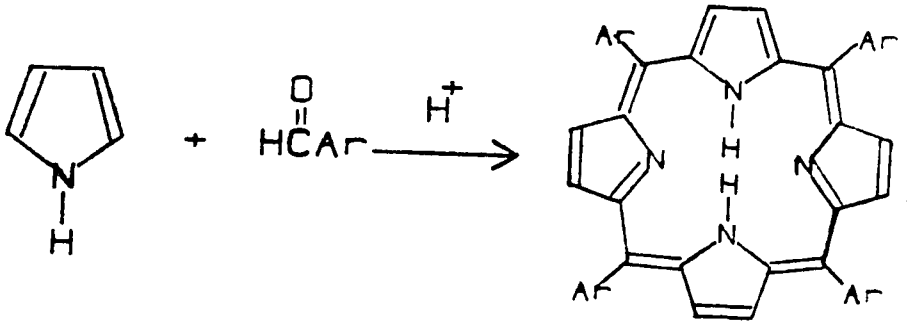


46

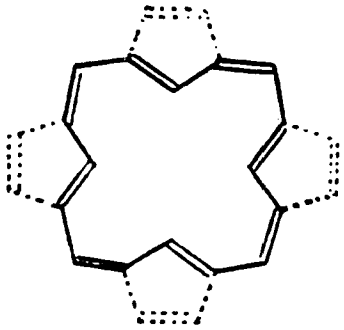
Tetra(aryl)porphyrins (**47**) have been widely used as models for naturally occurring porphyrins because of their ease of preparation. *Meso*-tetrasubstituted porphyrins were first prepared by Rothemund, in 1935, by heating a mixture of pyrrole, an aldehyde, and pyridine in a sealed tube.[70] This "Rothemund" condensation has been widely used in the preparation of numerous *meso*-substituted porphyrins,[71] which contain a symmetric substitution pattern. Because of the potential for isomer formation, the preparation of substituted tetra(aryl)porphyrins by direct substitution of a tetraphenylporphyrin has received little attention. These macromolecules would be interesting as starting materials for hemoprotein models, if an efficient regioselective synthesis was developed.



47

Porphycene (**55**)[72] is a new series of porphynoid species, and is regarded as an NH-bridged [18]-annulene. The dianion of [16]annulene **48** corresponds, both in geometric and electronic respects, to the central 16-membered ring of the dianion of **49**. Similarly, the dianion of the hypothetical [16]annulene (**51**),

possessing the periphery of 1,6:9,14-bismethano[16]annulene (50), is related to the dianion of a structural isomer of porphyrin.



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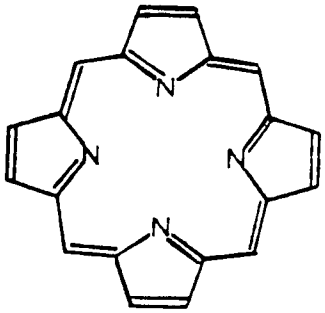

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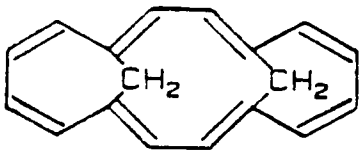

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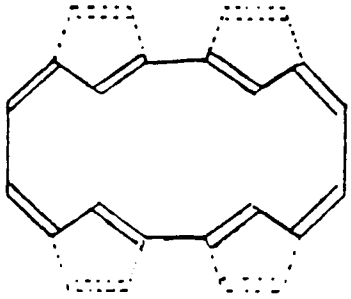

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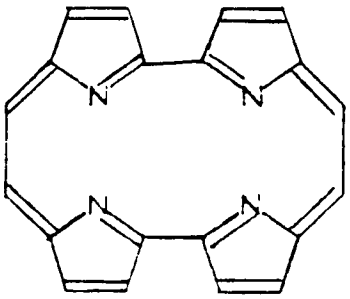
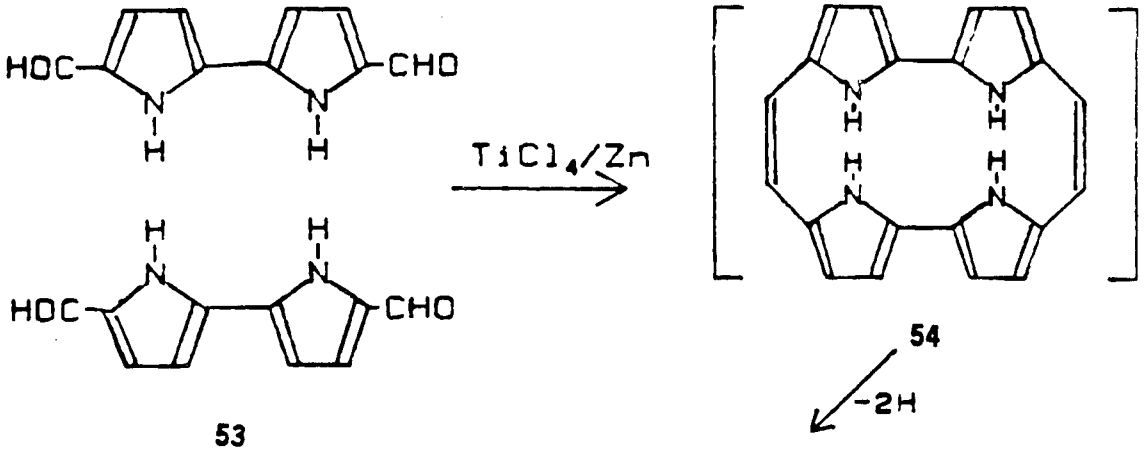


52

To synthesize porphycene **55**, 5,5′-diformyl-2,2′-dipyrrole (53) was refluxed for 4 hours with a slurry of a low-valent titanium reagent in pyridine/THF. An interesting feature of this synthesis is that the presumed intermediate **54** rapidly loses two hydrogen atoms in the reducing environment. Porphycene (**55**), which sublimes above 250°C with virtually no decomposition, dissolves in organic solvents to give blue solutions showing red-violet fluorescence. ^{1}H NMR of **55** shows an NH tautomerism, rapid on the NMR time-scale, which is suggestive of strong intramolecular N-H··N hydrogen bonding, expected of a planar molecule. According to an X-ray

structure analysis (Fig. 9), **55** was centro-symmetric (on the average) and, like porphyrin, virtually planar. It is not possible to assign the two imino hydrogen atoms unequivocally to specific nitrogen atoms.



53 **54** **55**

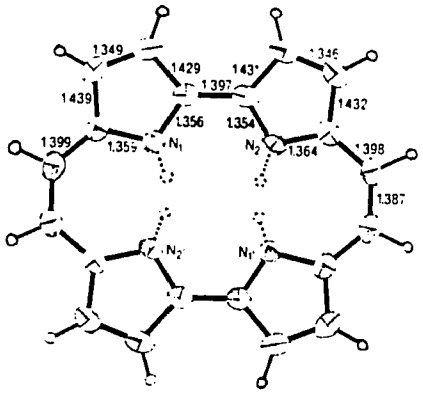
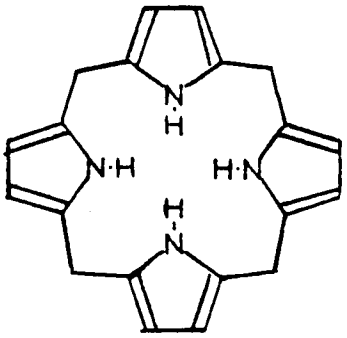


Fig. 9. X-ray Crystallographic Structure of Porphycene **55**.

III-3. Xanthoporphinogens

The porphyrinogens (**56**), which are colorless cyclic tetrapyrrylmethanes or *meso*-hexahydroporphyrins, are important precursors to porphyrins, both *via* biosynthesis and the Rothemund condensation. Fisher developed numerous methods for the reduction of porphyrins to porphyrinogens:[73] sodium amalgam, phosphonium iodide, and catalytic hydrogenation with Raney nickel. Photoreduction of porphyrins with mild reducing agents,[74] such as EDTA and glutathione, leads to phlorins **57**, while strong reducing agents (titanous or chromous chloride) result in the formation of porphomethenes (tetrahydroporphyrins, **58**). Porphyrins are most likely photoreduced to the porphyrinogen stage with acidic stannous chloride and ascorbic acid. However, porphyrinogens (**56**) are easily reoxidized to the parent porphyrins.



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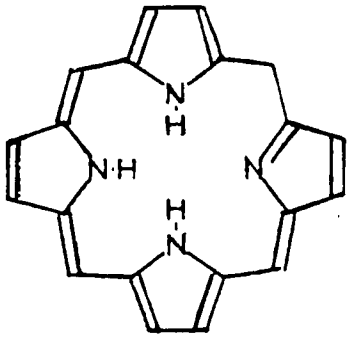

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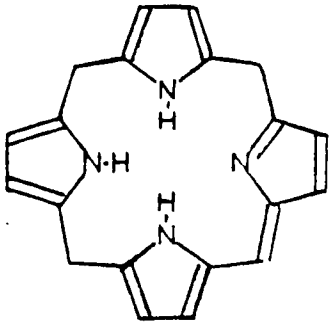
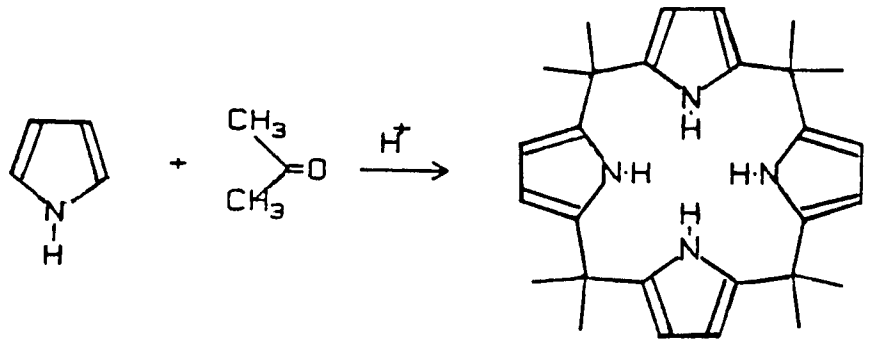


58

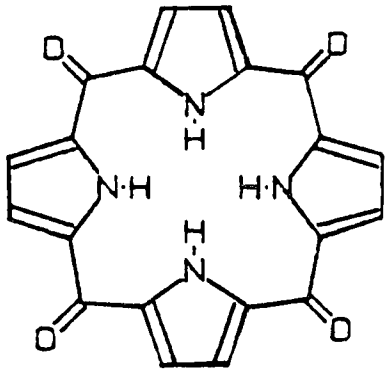
The first documented macrocycle possessing a pyrrole subheterocyclic ring was reported in 1886 by Baeyer[75] *via* the condensation of pyrrole and acetone in the presence of mineral acid to give the non-oxidizable acetopyrrole **59** in high yield. Rothemund[76] showed that at least three of the four *C*-bridges are α-linked to the pyrrole; the structure of **59** was later reassigned by Brown *et al.*[77]



59

Munich *et al.* reported the formation of tetrapyrrolic derivatives called "xanthoporphyrinogens" derived from a range of

porphyrins upon treatment with lead dioxide in acetic acid.[78] These workers considered the products to be tetraketone **60**, which was confirmed recently by Inhoffen *et al.*[79] *via* X-ray analysis. Ketotetrapyrroles with oxidation levels between those of oxophlorins and xanthoporphyrinogens have also been reported.[80]



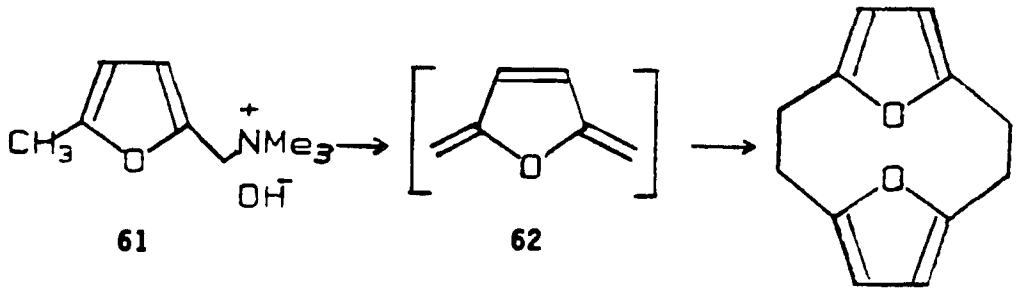
60

III-4. (2,5)Furanophanes

Continuous interest[81] in macrocycles containing furan rings has spaned more than three decades; however, often the inclusion of the furan ring has been merely for structural interest in which the work was directed elsewhere, even though the furan ring is one of the important heterocycles in natural products.

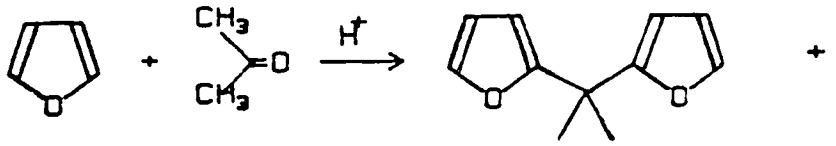
Of the *C*-bridged furanophanes, [2•2](2,5)furanophane (**63**) has been the most widely investigated. Generally these furanophanes are synthesized by the 1,6-Hofmann elimination. Winberg *et al.*[35] used this method to prepare the first reported [2•2](2,5)furanophanes *via* the pyrolysis of (5-methyl-2-furfuryl)trimethylammonium

hydroxide (61). The key intermediate 2,5-dimethylene-2,5-dihydrofuran (62) was trapped at -78°C and upon warming in the presence of radical inhibitors 62 dimerized (73%) to form 63, as well as a 1,6-coupled polymer possessing rearomatized furan rings.

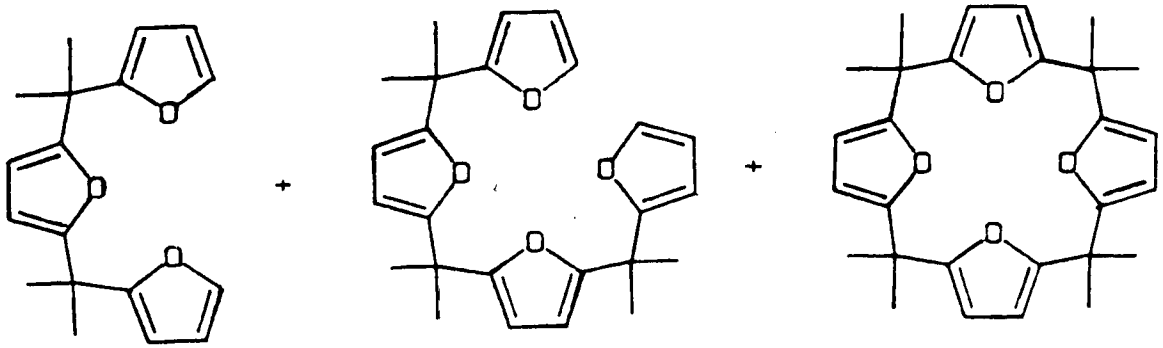


61 62 63

One of the largest classes of furan-containing macrocycles is that of *tetraoxaquaterene*.[82] [*Quaterene* denotes a macrocycle composed of four methylene-bridged 1,4-disubstituted cyclopentadienes.] A study of the acid-catalyzed condensation of furan with numerous acyclic ketones and aldehydes has been reported by Brown and co-workers.[82,83] In general, when ketones, e.g. acetone, were condensed with furan under the appropriate conditions (excess furan), 64-67 were generated; however, with excess acetone, only 67 was obtained. The mechanism of this sequence has been studied in detail by Brown *et al.*[77] In general, such condensations have given rise to predominantly polymeric products; however enhanced yields (ca. 20%) of the desired macrocycles can be realized when metal ions are added to the reaction (the template effect).[84] An alternative observation, recently forwarded[85a,c] by Rest and others[85b], correlated the yield of the macrocycles, not with the metal ion content but with the amount of added acid. Numerous

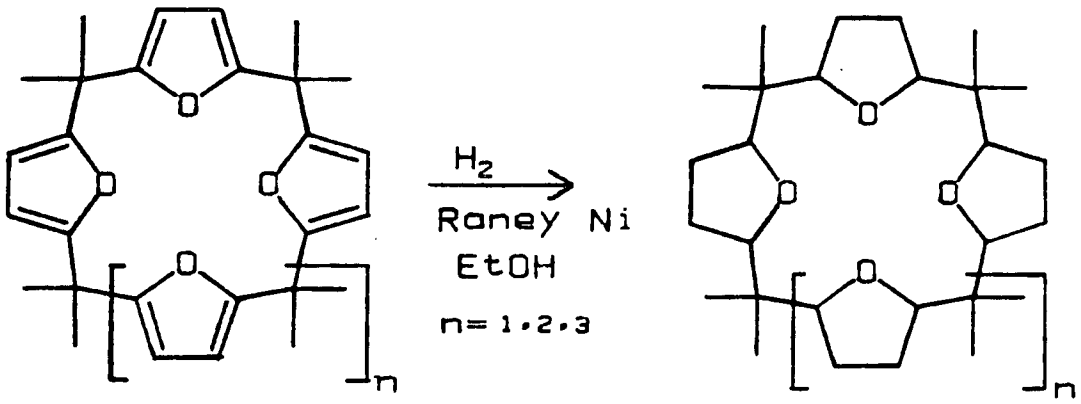


64



65 66 67

intermediates have been isolated, which, in certain cases, can be subsequently converted to the desired macrocycle, when subjected to additional acidic conditions.



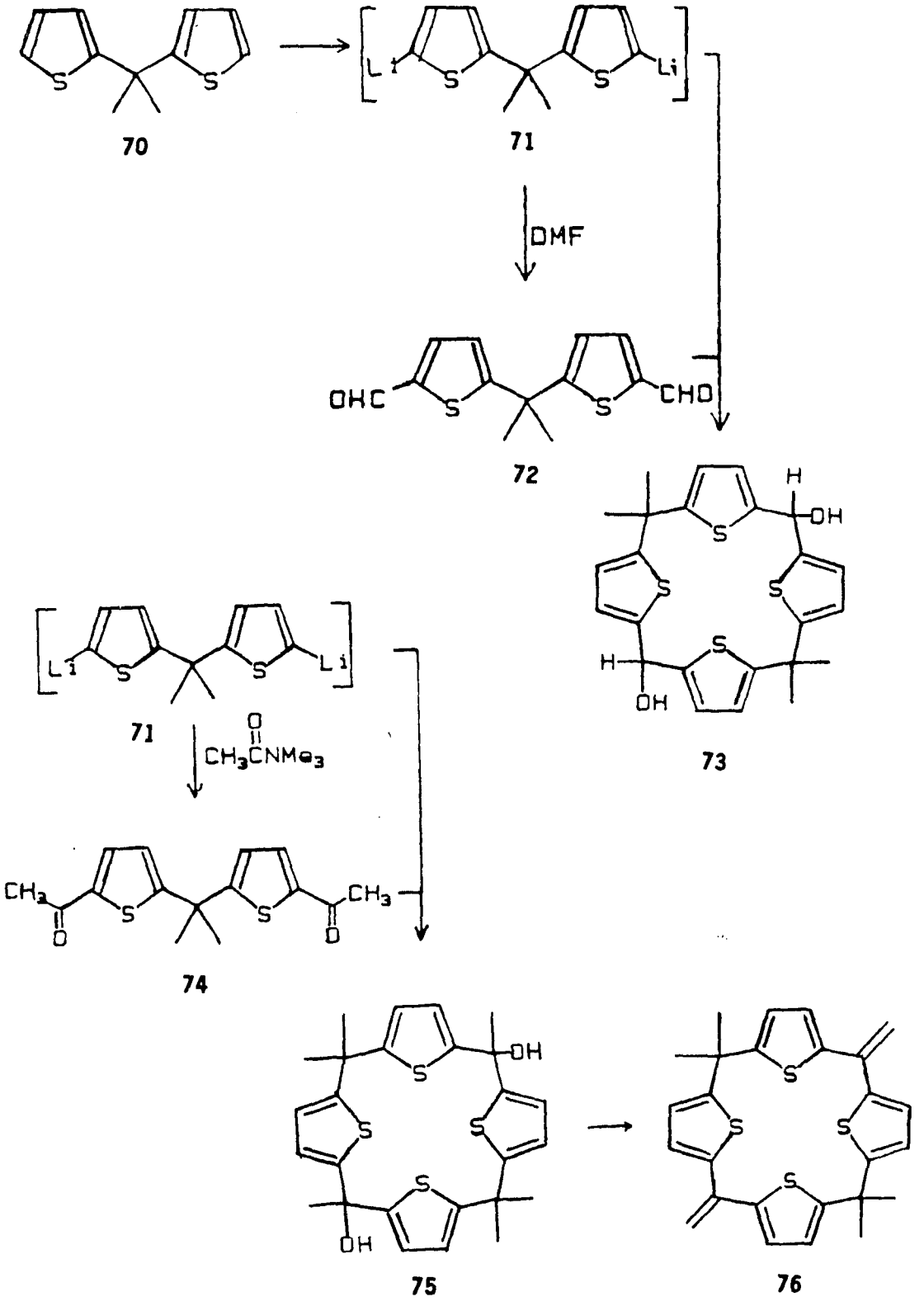
68 69

Since certain antibiotic ionophores, e.g., actins, nigericin, and monensin, contain tetrahydrofuran units, tetrahydrofuran was thought to have a potential utility as a macrocyclic chain component because of its donor ability as well as its hydrophilic and lipophilic balance. The synthesis of the tetrameric tetrahydrofuran-acetone macrocycle **69** from **68** was reported to occur in absolute ethyl alcohol.[84a,86]

III-5. (2,5)Thiophenophanes

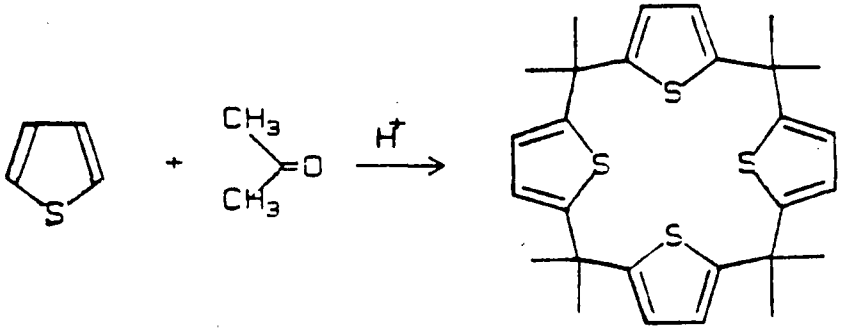
Although the chemistry and syntheses of the porphyrin ring system have been intensively investigated for more than a century, few reports have appeared regarding its thiophene isosters. Pyrrole and furan when treated with acetone and hydrochloric acid generated porphyrinogen and tetraoxaquaterene, respectively; however, initial attempts to prepare tetrathioquaterene **77** in an analogous manner failed.[83c]

The first synthesis of thiophene isoster **73** of the porphyrinogen system was reported by Ahmed and Meth-Cohn[87] by the action of *n*-BuLi under high dilution conditions. However, the interaction of dilithiodithienylmethane **71** with methyl formate failed to afford the desired product; thus to eliminate the possibility of bridge metallation, di-2-thienylpropane (**70**, R=H) was used. With the corresponding dilithio derivative **71**, the diformyl **72** yielded (4.2%) dihydroxytetramethylthiaporphyrinogen (**73**), while **74** gave (2.5%) the corresponding hexamethyl analogue


70
71
DMF
OHC
CHO
72
H
OH
H
OH
73
71
CH3CNMe3
CH3
CH3
74
OH
OH
75
76

75. Isolation (0.8%) of diolefin **76** could be attributed to dehydration of alcohol **75** during chromatography over silica gel.

The 'one-step,'simple acid-catalyzed cyclocondensation of thiophene with acetone under rigorous conditions with mineral acid to give **77** has been reported.[88]



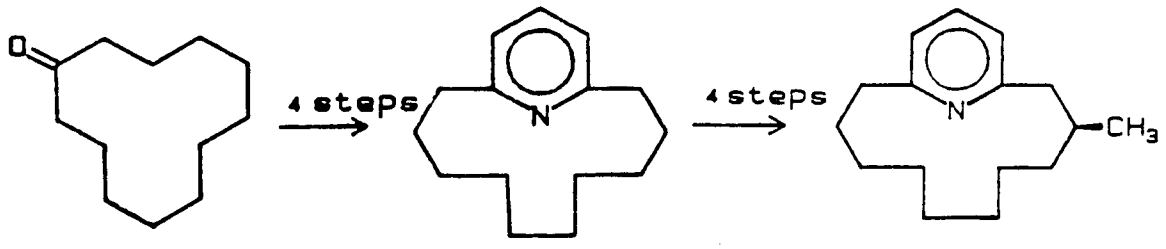
77

III-6. (2,6)Pyridinophanes

There is abundant evidence that pyridine is an electron-deficient aromatic molecule, with a resonance energy comparable to that of benzene. Its chemistry does not resemble that of benzene in that there are many important differences which are due to the presence of the ring nitrogen atom (details in Chap. IV).

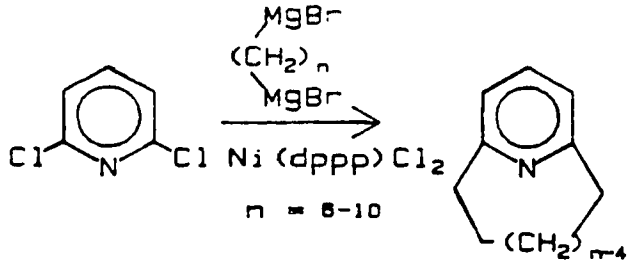
The first (2,6)pyridinophane studied was that of 9-methyl[10]-(2,6)pyridinophane (**78**, trivial name "muscopyridine"). This substance, the most widely known naturally-occurring pyridine macrocycle, first isolated in 1947 by Prelog *et al.*[62] from the

scene gland of the musk deer, was subsequently synthesized in 1957 *via* a multistep synthesis by Büchi, *et al.*[89] from cyclododecanone.



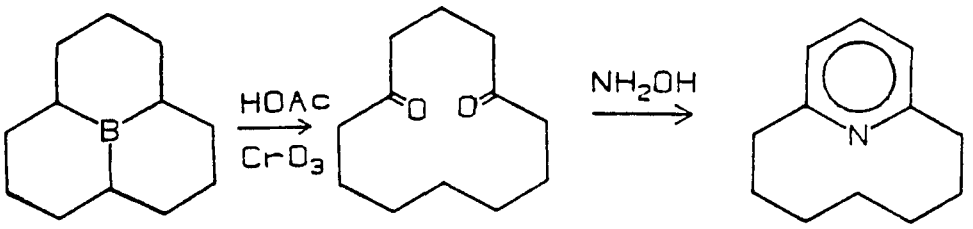
78

The one-step construction of racemic muscopyridine has been accomplished *via* cyclocoupling the di-Grignard of 2-methyl-1,10-dibromodecane with 2,6-dichloropyridine in the presence of a catalytic amount of a nickel phosphine complex [Ni(dppp)Cl_2].[90] This cyclocoupling was also successful in the preparation of several other [N](2,6)pyridinophanes (79).



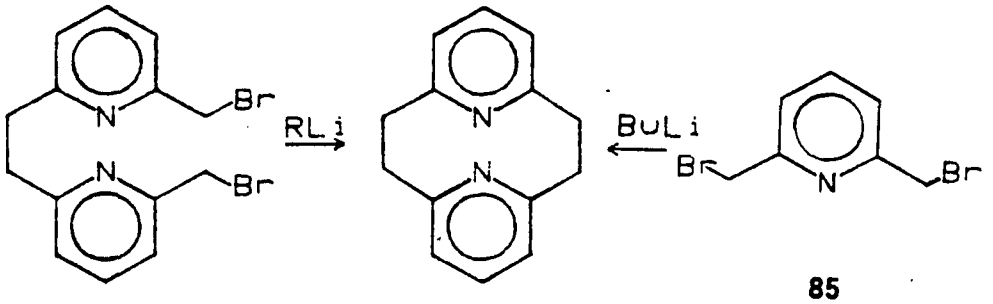
79

Alternatively, a pyridine subring can be prepared from precursors to the pyridylium salt, i.e., 1,5-diketones. 1,5-Cyclododecanedione (81), prepared from boraperhydrophenalene (80), with hydroxylamine generated the [7](2,6)pyridinophane (82).[91]



80 **81** **82**

The synthesis of multimembered pyridinophanes, [2.2](2,6)-pyridinophane (**84**) was first reported by Baker et al.[92] through cyclization of 1,2-bis(6′-bromomethyl-2′-pyridyl)ethane (**83**) by action of either *n*-butyllithium in ether or phenyllithium in benzene/ether. [2.2](2,6)Pyridinophane (**84**) was also prepared in a similar manner *via* treatment of the corresponding dibromide **85** with butyllithium.[94]

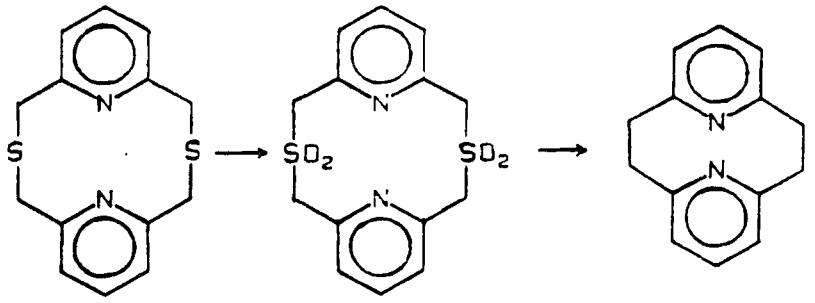


83 **84** **85**

Sulfur extrusions may fall under the more general class of symmetry-controlled processes, known as cheleotropic reactions;[33a] however, the concerted process requires a precise location of double bonds with respect to the species being extruded.[33,94] Since carbon-sulfur bridged macrocycles **86** were easily prepared by

standard basic conditions,[33] their conversion to the *C*-bridged species was important. Three different syntheses of pyridinophanes from dithiacyclophane precursors by *S*-expulsion have been reported.[33,94]

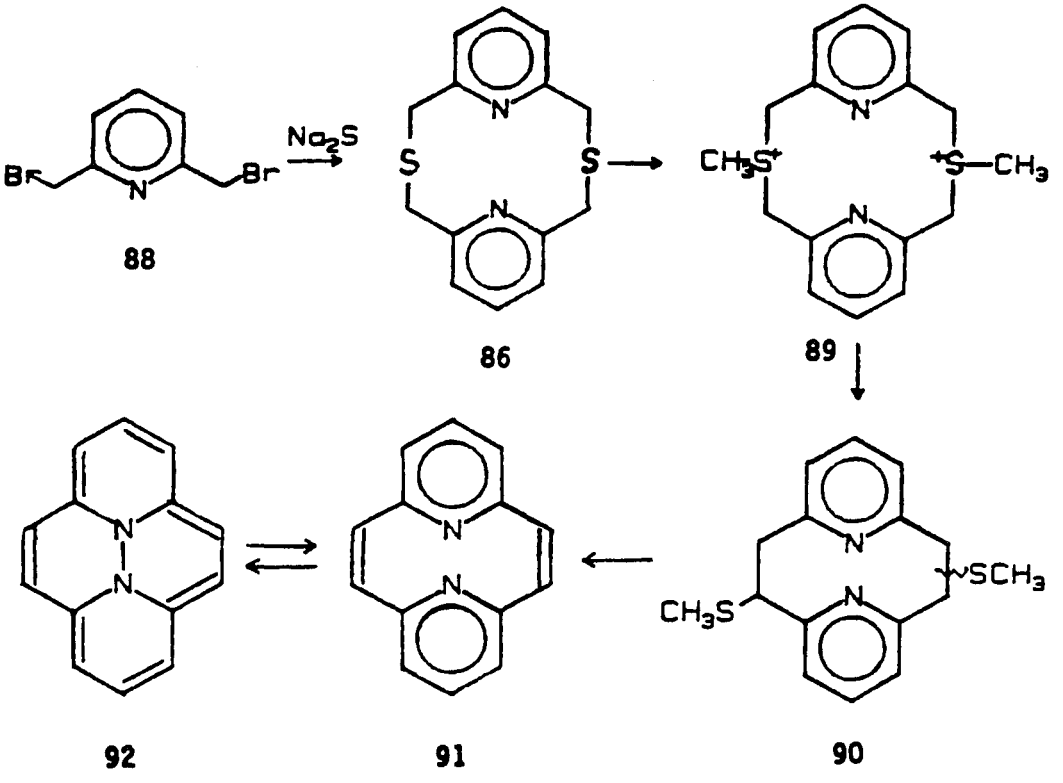
a) **Thermal expulsion of sulfur dioxide from the corresponding sulfone**, called "sulfone pyrolysis", has been expanded into a generally applicable method, even permitting the synthesis of sterically strained medium- and multi-membered cyclic and polycyclic systems containing aromatic rings.[95] For example, *bis*-sulfone **87**, which was prepared from **86** *via* oxidation, can be converted into [2•2](2,6)pyridinophane (**84**) by the use of high temperature at low pressure.[96]



86 **87** **84**

b) **The two-step extrusion of sulfur by a Stevens' rearrangement, followed by a Hoffmann elimination**, was reported by Boekelheide and Lawson[97] for the preparation of **89**, in which initially 2,6-*bis*(bromomethyl)pyridine (**88**) with sodium sulfide gave a dithia[3•3]pyridinophane (**86**). Subsequent dimethylation of **86** using Meerwein's reagent (trimethyloxonium tetrafluoroborate)

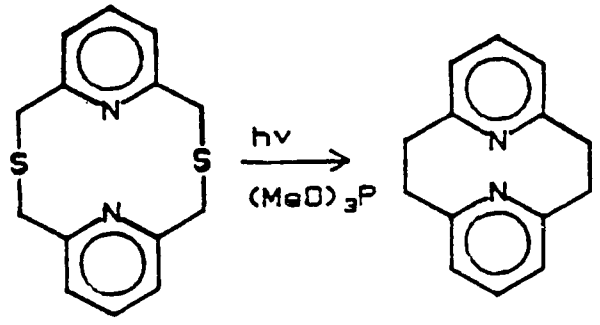
afforded the crude methylated product **89**, which upon treatment with potassium *t*-butoxide effected a Stevens' rearrangement to give **90**. Modification of this two-step procedure by using 2,6-di(*tert*-butyl)phenoxide, as the base, gave rise to **91**. The spectral data, obtained for the isolated product, indicated[94] that this cyclophane exists as **91** and not as its valence tautomer **92**. Studies also showed that under aqueous acidic conditions, **91** acted as a normal base and that there was no indication of an acid-catalyzed valence-tautomerization to **92**.



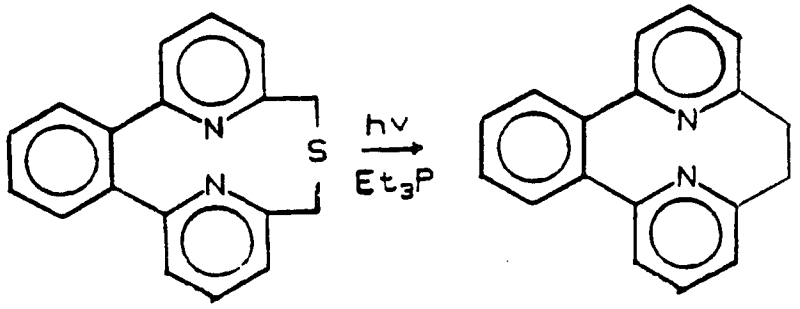
88 **86** **89** **90** **91** **92**

c) The irradiation of sulfides in the presence of a trialkylphosphite promotes photochemical *S*-extrusion from a sulfide. This

approach may be the most convenient synthetic method for pyridinophanes, as demonstrated by the irradiation of **86** in trimethoxyphosphite at 25°C to generate **84**.[98] With the similar procedure, the synthesis of **93** was succeeded by initial formation of the cyclic sulfides, then *S*-extrusion by irradiation in the presence of triethylphosphite.[99]



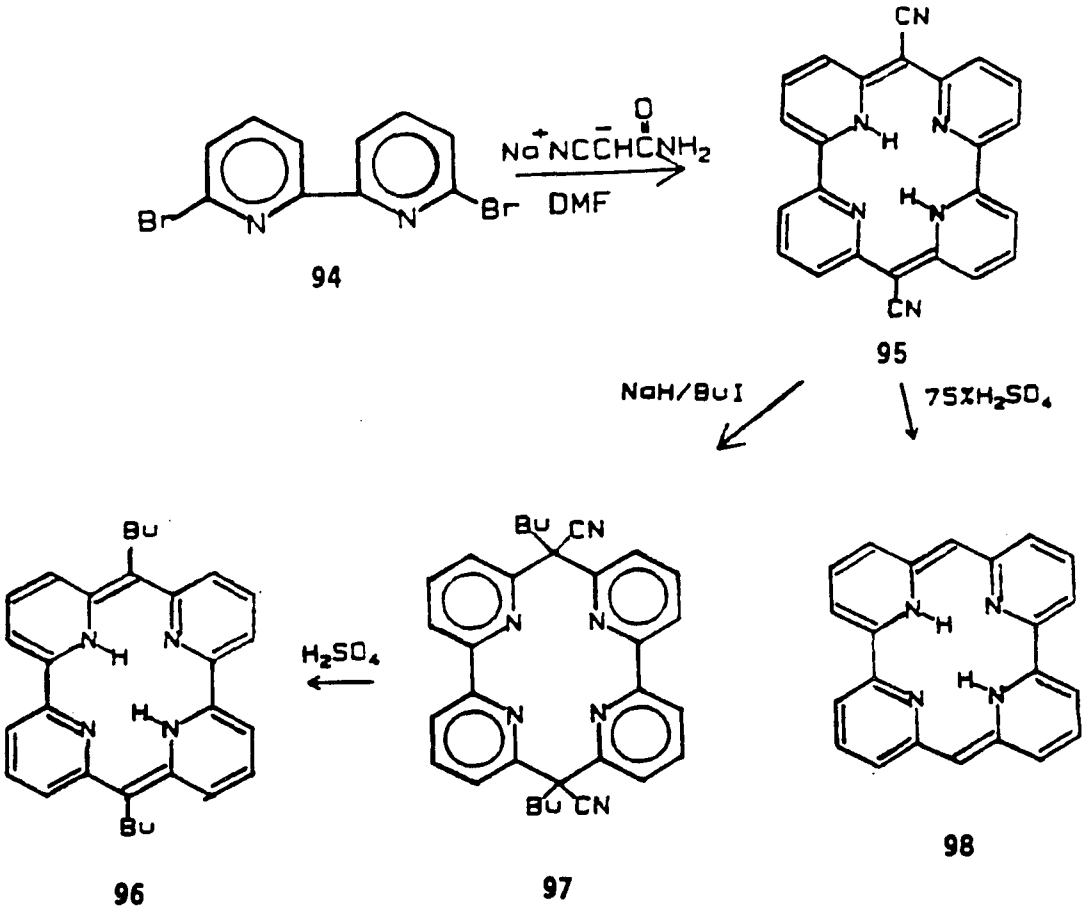
86 **84**



93

Recently, an elegant synthesis for the construction of 2-pyridyl-2(1*H*)-pyridylideneacetonitrile (**95**)[100] was reported in which the sodium salt of α-cyanoacetamide in DMF was reacted with 6,6′-dibromo-2,2′-bipyridine (**94**).[101] Red dicyano macrocycle **95** could be hydrolyzed and decarboxylated with 70% sulfuric acid to give dark-red tetraaza **96**. Alkylation of **95** was accomplished successfully by treatment with 1-iodobutane and sodium hydride to

afford (30%) colorless dibutyl dicyano **97**; subsequent treatment of **97** with 70% sulfuric acid provided (60%) red dibutyl **98**. It is noteworthy that while tetrasubstituted **97** is colorless, the other macrocycles (**95**, **96**, and **98**) are favored for deep-red fully conjugated methine forms (details in Chap. VII).



IV. Nitrile-Stabilized Nucleophiles

IV-1. Nucleophilic Substitution on Pyridines

Pyridine is the most electron-rich of the electron-deficient heterocycles. It has a high resonance energy and its structure closely resembles that of benzene. The presence of the ring nitrogen atom does, of course, represent a major perturbation of the benzene structure.[17] The lone pair in the plane of the ring provides a nucleophilic site for protonation and alkylation, which has no analog in benzene. Many of the properties of pyridine are those of a tertiary amine and thus never directly involve the aromatic sextet. The other major influence of the nitrogen atom is to distort the electron distribution in both the π-bonding system and σ-bonds (*via* an inductive effect). This confers on the ring, polarization similar to that associated with conjugated imines or conjugated carbonyl compounds. The distortion of electron distribution is greater still in quaternary pyridinium salts.

It is convenient to classify reactions[60] of pyridines and pyridinium salts according to analogies to those of three model types: (a) Tertiary amines:[88] reactions at the *N*-lone pair, including protonation, alkylation, acylation, *N*-oxide formation, and coordination to Lewis acids; (b) Benzene: substitution reactions and resistance to addition and ring-opening; (c) Conjugated imines or carbonyl compounds: susceptibility to

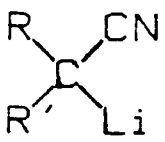
nucleophilic attack at the α-positions. This last analog has important consequences for the nature and type of substitution that pyridines can undergo.

Electrophilic substitution,[102] which typifies benzene chemistry, is not common with pyridines. First, the kinetic reaction product of pyridine with an electrophile is that in which the electrophile is *N*-coordinated. This makes electrophilic substitution at carbon even more difficult, because further reaction has to take place either on the pyridinium salt or on the uncomplexed pyridine, which may be present. Second, *C*-attack of an electrophile is selective; it tends to go mainly at the β-positions, which have the greatest π-electron density (see Chap. III). Attack at these β-positions also leads to the formation of intermediates, which are destabilized by the presence of the ring nitrogen. This is analogous to the preferred *meta*—substitution of deactivated benzene derivatives, such as nitrobenzene, by electrophiles.

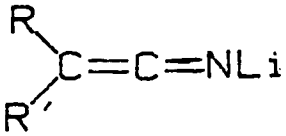
Even though nucleophilic substitution is not a common process in benzene chemistry, it occurs easier in pyridines, particularly at the α- and γ-positions, which are activated by the ring nitrogen. Thus, nucleophilic displacement of a good leaving group *including hydrogen* by an addition-elimination mechanism occurs most readily for leaving groups at the α- and γ-positions. As a consequence of their π-deficient nature, pyridines undergo nucleophilic substitution more readily than benzene.

IV-2. Nitrile-Stabilized Carbanions

The utilization of carbanions, which are stabilized by various electron-withdrawing groups, to effect *C-C*-bond formation is important in organic synthesis. Among these carbanions, deprotonation of primary or secondary nitriles with an array of different bases constitutes the most convenient method for generating mono-α-anions of nitriles. Successful addition and substitution reactions of nitriles depend critically on the generation of the nitrile-stabilized carbanion represented typically by the tautomeric structures **99a** and **b**. This brief section focuses on the reactions of nitrile-stabilized carbanions[103] with an array of *C*-electrophiles. Since detailed studies on the acidity of various nitriles are available only in dimethyl sulfoxide solution,[104,105] the following discussion focuses on comparisions in that solvent.



99a



99b

Although acetonitrile (pK_a 31.3) is a relatively weak acid in comparision to other carbon acids bearing electron-withdrawing groups, various substituents exert a dramatic influence on pK_a values. The introduction of additional phenyl groups substantially lowers the pK_a values as shown in Table 1: 9-cyanofluorene <

diphenylacetonitrile < phenylacetonitrile < acetonitrile. The magnitude of the pK_a differential between phenylacetonitrile and acetonitrile is considerably greater than the difference of pK_a for phenyl-substitution in nitromethane or acetophenone.[104c] This large differential in the acetonitrile series is ascribed to less negative charge residing at the nitrogen atom in the acetonitrile anion than at the more electronegative oxygen atom in the nitromethane or acetophenone anions. The addition of a second phenyl group exerts a less dramatic effect, as a result of steric inhibition of resonance. [Other (hetero)arylsubstituted acetonitriles possess acidities comparable to phenylaceto-nitrile.]

Table 1. Acidity of Nitriles in Dimethyl Sulfoxide Solution.[104,105]

	pk_a
Propionitrile	32.5
Acetonitrile	31.3
2-Phenylpropionitrile	23.0
Phenylacetonitrile	21.9
2-Furylacetonitrile	21.3
2-Thienylacetonitrile	21.1
1-Naphthylacetonitrile	20.8
2-Naphthylacetonitrile	20.6
Diphenylacetonitrile	17.5
9-Cyanofluorene	8.3

In contrast to phenyl groups, methyl substitution in acetonitrile *decreases* the acidity of the α-hydrogens, as illustrated by comparision of acetonitrile and propionitrile or phenylacetonitrile and 2-phenylpropionitrile. This destabilizing influence originates in the inductive electron release from methyl, relative to hydrogen, to the sp^2-carbon of the anion.[104c] This result parallels the suggested decrease in the rate of deprotonation of nitriles: $CH_3CN > CH_3CH_2CN > (CH_3)_2CHCN$ and contrasts with the inverse relationship for rates of proton abstraction and acidity for similarly substituted nitromethanes.[105] Such findings underscore the difficulties in assigning relative α-carbanion stabilities from kinetic measurements alone.

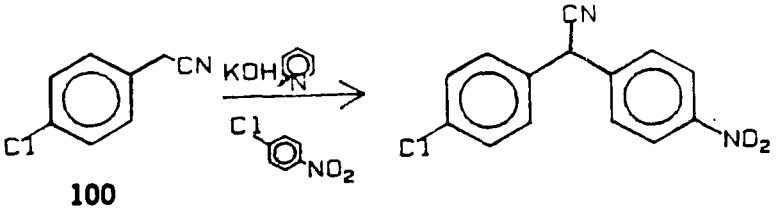
IV-3. Nitrile-Stabilized Nucleophiles

The reactions of nitrile-stabilized α-carbanions are grouped according to the nature of substituents, such as alkyl, alkenyl, alkynyl, and aryl groups as well as various α-oriented halogen-, oxygen-, nitrogen-, sulfur-, and selenium-containing groups. The effect[104a] of common electron-withdrawing groups on carbanion stability is hence on the acidity of the conjugated acids, thus: $NO_2 >> RCO > RSO_2 > CN$.

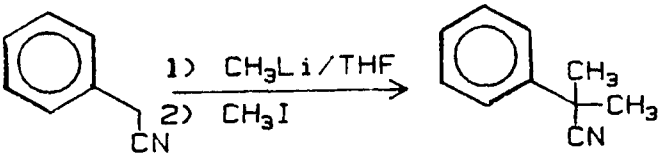
Selection of an appropriate base for a given pK_a range guarantees a high concentration of the requisite nitrile-stabilized carbanion and minimizes side reactions that can intervene when the nitrile and its anion coexist in solution. Since the pK_a of the

nitriles span over 20 pK_a units, the base is usually selected to reflect the acidity range of the particular nitrile. In general, with the most acidic nitriles including the (hetero)arylaceto-nitriles, weak bases, in particular sodium hydroxide under phase-transfer conditions, are adequate for deprotonation. The less acidic aliphatic nitriles generally require alkali metal amides and metal alkyls, as bases.[103]

C-Alkylation of 4-chlorophenylacetonitrile (100) with 4-chloronitrobenzene using KOH in pyridine was investigated by Davis and Pizzini.[106] Alkyl (or aryl) metal reagents were generally used to metalate nitriles. Their use may be complicated by competitive addition of the organometallic reagent to the nitrile moiety.[107a] In general, successful alkylations, as illustrated by preparation of **101**,[107b] using organometallic reagents, as bases, involved the preparation of tertiary nitriles and employed low temperatures to avoid competitive nitrile addition reactions.



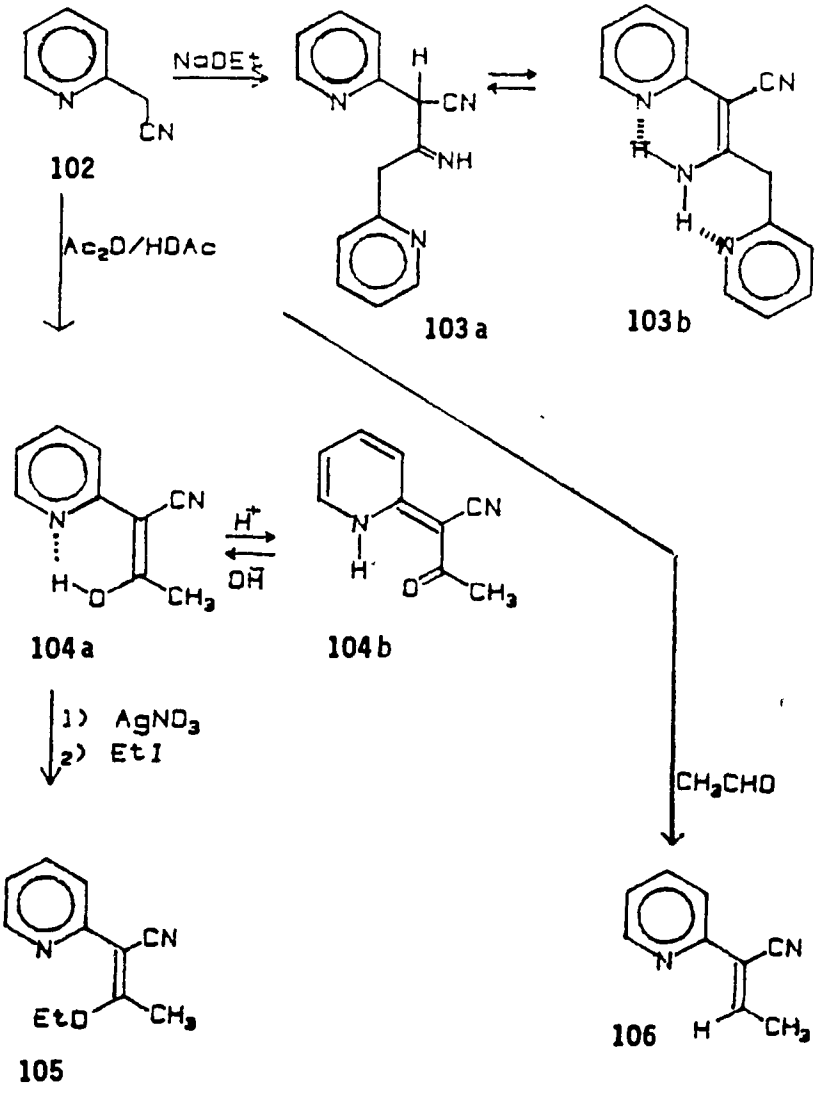
100



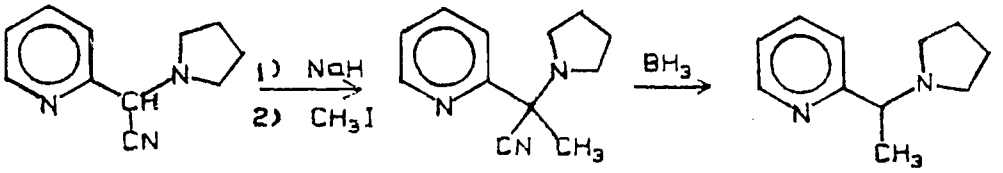
101

α-Carbanion formation of 2-pyridylacetonitrile (102) has been reported by Gutsche and Voges.[108] When **102** was heated with

ethanolic ethoxide, it was converted to a dimer **103a** (presumably tautomer **103b** was also present but not completely characterized). Treatment of **102** with acetic anhydride/acetic acid gave **104**; the tautomeric equilibrium between **104a** and **104b** was dependant on pH. An ethyl derivative **105** was formed when the silver salt of **104** was treated with ethyl iodide. When **102** was heated with acetaldehyde and a base, it underwent the expected Knoevenagel reaction to give **106**.

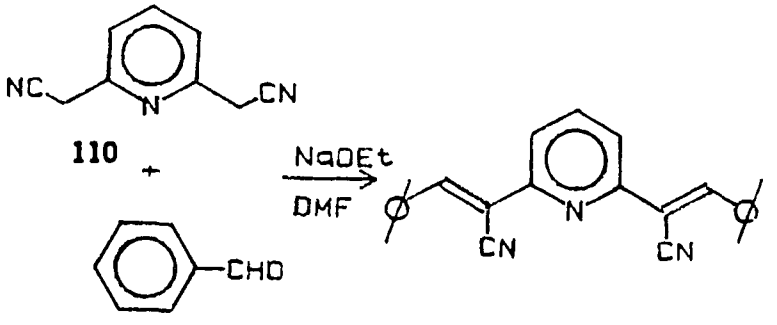


As part of their studies involving the structure and reactivity of nicotine and various analogues, Sanders et al.[109] treated α-cyanoamine **107** (from 2-pyridinecarboxaldehyde, pyrrolidine, and KCN) with NaH and CH_3I to give **108**, which underwent subsequent reductive cleavage with BH_3 to generate **109**.



107 **108** **109**

2,6-Pyridineacetonitrile (**110**) was condensed with benzaldehyde to afford **111**; no yield and isomer data were reported.[110] Under the same conditions, **110** reacted with terephthalaldehyde to afford polymers.

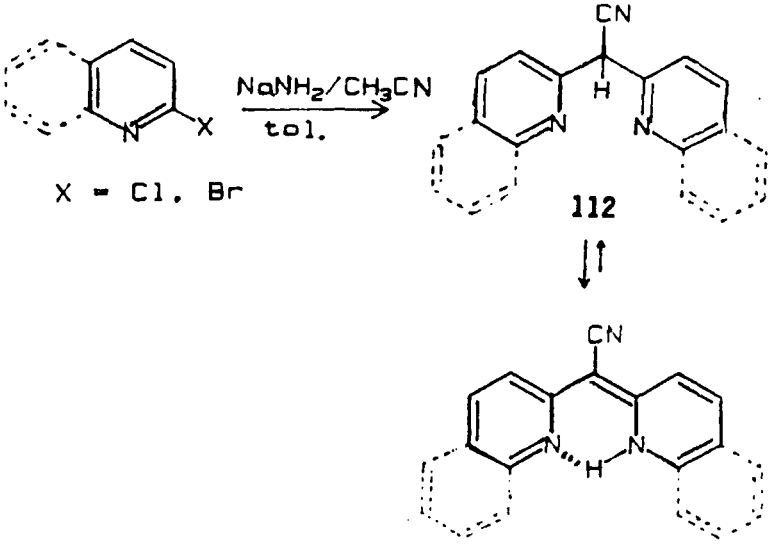


110 **111**

Although nucleophilic substitution with 2-pyridylacetonitrile has not been investigated to any great extent, acetonitrile, as a

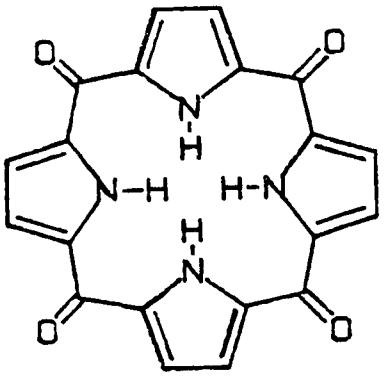
nucleophilic reagent has been studied systematically.[103,111] Successful monoalkylation of acetonitrile initially utilized strong bases, such as alkali metal hydrides, amides, dialkylamides, or *bis*(trimethylsilyl)amides, to generate high concentrations of the requisite nitrile anions, then reactive primary or secondary alkyl halides were used to intercept the desired carbanion.

Alkaline metal acetonitrile anions were used as nucleophiles in the reaction with 2-bromopyridine (or 2-chloroquinoline).[102,112] A characteristic feature of these acetonitrile derivatives was that the acidity of the α-proton led to the formation of the dominant tautomer, a mesomerically-stabilized, colored form, by intramolecular proton shift, followed by rehybridization of sp^3 to sp^2. Direct NMR spectroscopic evidence[113] for these methine tautomers was shown for *bis*(2-pyridyl)acetonitrile (112), since the N-*H* proton was observed at δ16.3 ppm and the ^{13}C NMR of methine bridged carbon appeared at δ67.5 ppm (details in Chap. VII).

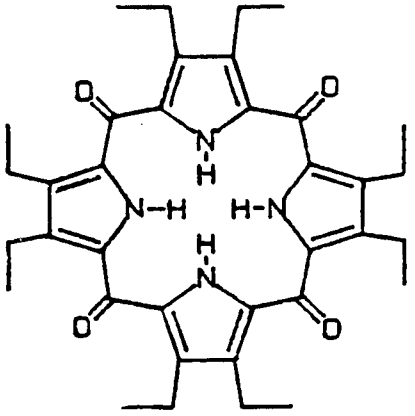


V. Proposed Research

Xanthoporphyrinogen (60) is a yellow, tetraoxygenated product formed by oxidation of porphyrins with lead dioxide. Although Fischer and Orth[78] discussed the tetraoxophorphyrinogen (113), as a possible structure, it was only 20 years ago that Inhoffen et al.[79] was able to confirm its structure by X-ray analysis. The difficulties in assigning a structure to 113 was mainly due to the puzzling chemistry of the molecule, since (a) steric hindrance of the neighboring β-pyrrolic substituents interferes with derivatization of the *meso*-carbonyl groups; (b) strong binding of two water (or solvent) molecules were observed in the clathrate-type crystals;[114] and (c) differential reduction[115] of two, three or four of the carbonyl groups was experienced.



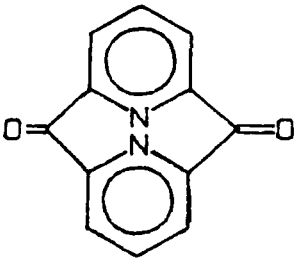
60



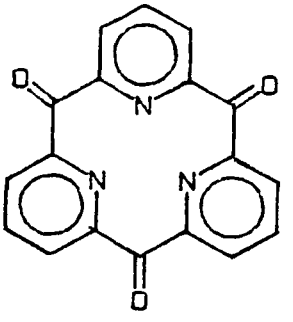
113

We were interested in preparing analogues of porphyrins, in which one or more of the pyrrole subunits were substituted by pyridine. The basic xanthoporphyrinogen framework was selected because connection of the 2,6-pyridino subunits with carbonyl groups offered considerable structural similarity to the naturally occurring systems and the synthetic design offered interesting challenges. Further, the carbonyl functionality can undergo a wide range of reductive transformations, thus analogs with substituents in the α-position are readily accessible.

The simplest member of this series is a diketone **114**; however, an 8-membered medium size ring was predicted to impose considerable strain energy on this molecule. A more realistic synthetic target is the next higher homolog - triketone **115**; its three heterocyclic (2,6-pyridino) rings are separated from one another by polarized, trigonal carbon atoms, and consequently the central cavity is electron rich. Thus, **115** should be a very effective proton sponge and excellent model to evaluate the effect of juxtaposed directed pairs of *N*-electrons. Inspection of a CPK molecular model of **115**



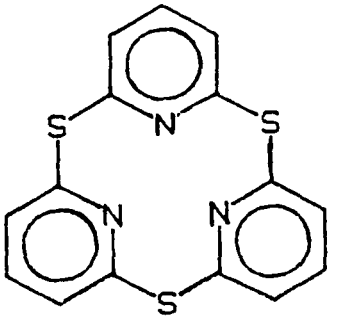
114



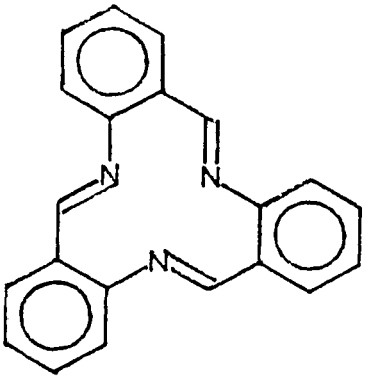
115

indicates that it will probably be planar or nearly so and an ideal structure to probe the electronic and/or steric effects within a highly electron-rich cavity. The only close relative of **115** is the trisulfide **116**,[116] which was found to have a nonplanar C_s conformation, due primarily to the constrained *C-S-C* bond angles. It is, however, not clear whether this nonplanarity is also in part a result *N*-lone pair electron repulsion or the small *C-S-C* angle (101.9°) imposed by the sulfur bridges.

Another structurally similar ligand, (tribenzo[*b*,*f*,*j*][1,5,9]-triazacycloduodecine) **117** was synthesized by Busch et al.[117a-c] *via* cyclocondensation of 2-aminobenzaldehyde in the presence of cobalt ions. Although the molecular model of **118** indicates there should be a close structural relationship between **115** and **117**, detailed studies[117d] indicate that **117** is a non-planar, highly flexible species.



116



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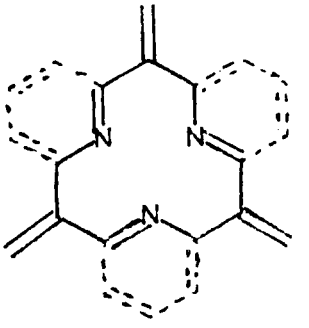
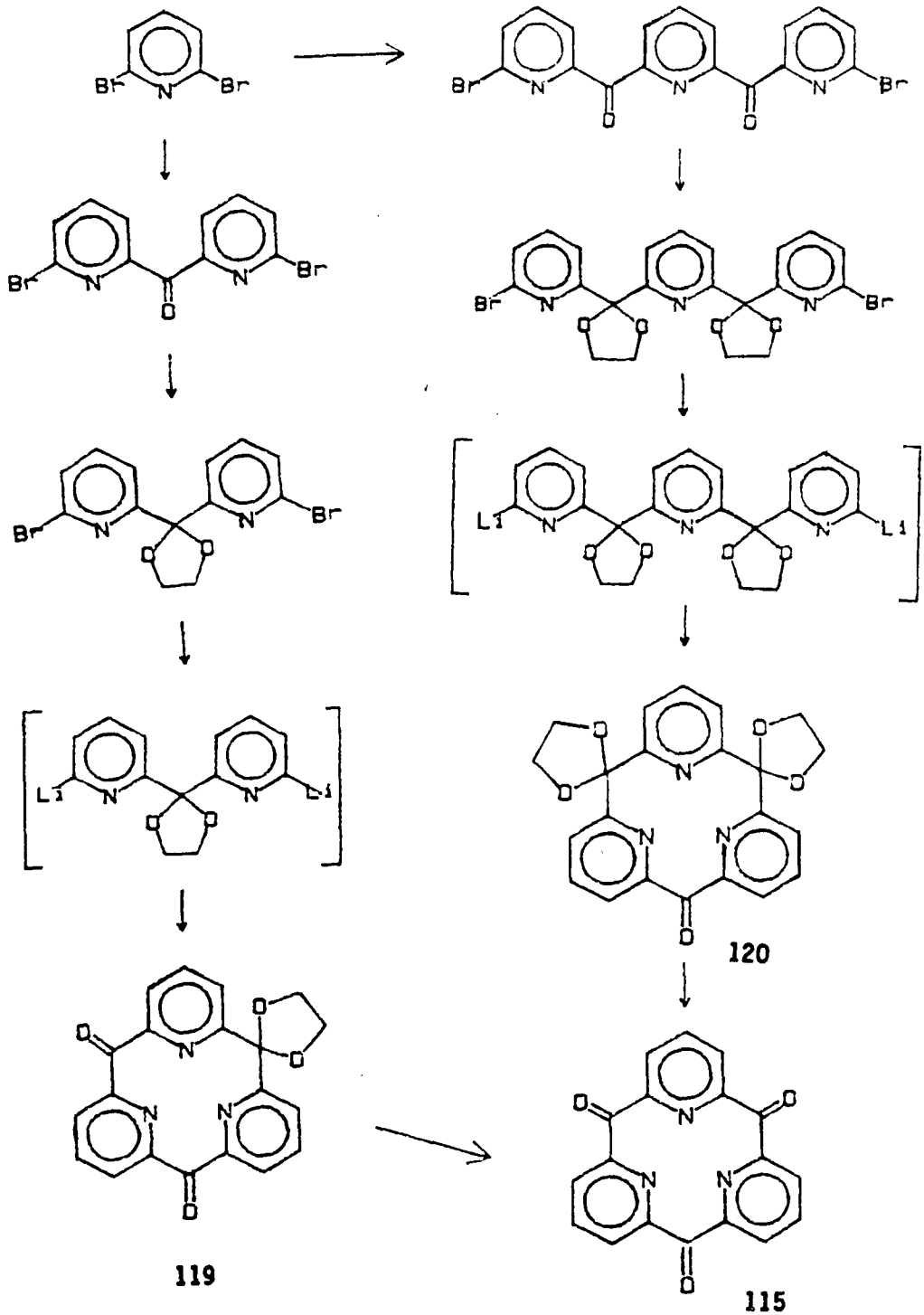


118

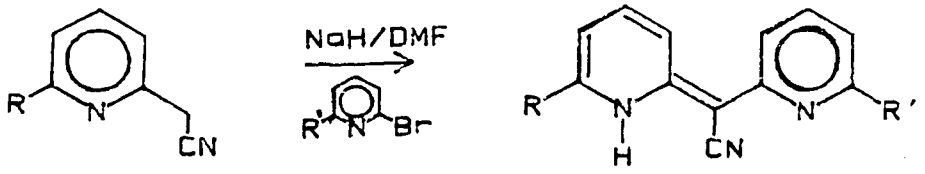
In 1978, Newkome et al.[118] reported the synthesis of **115** and demonstrated that it displays some of the characteristic structural features of the porphyrins. (Scheme 3) However, the yields of the

Scheme 3.

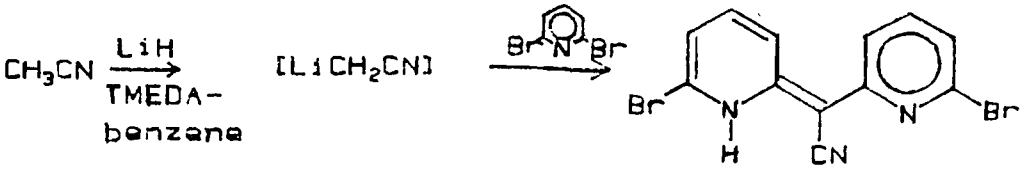


cyclocondensation step to generate triketone precursors (119 and 120) were very low. These decreased yields of 119 and 120 probably arose due to unwanted intramolecular complexation of the imine salt with the pyridyl nitrogen, which forms a conformationally unfavorable orientation, in which each nitrogen of pyridine rings was oriented *anti* to one of the dioxolane oxygens. The major products[119] were linear polymers of undetermined character.

Metalation of acetonitrile including its derivatives at high temperature and subsequent reaction with bromopyridines would generate the favorable intermediates (121 and 122)[120] necessary for condensation. An application of this nucleophilic substitution at elevated temperature for the synthesis of 115 (as outlined in Scheme 4) would have an obvious advantage; that is a favorable *syn*-orientation for cyclocondensation.

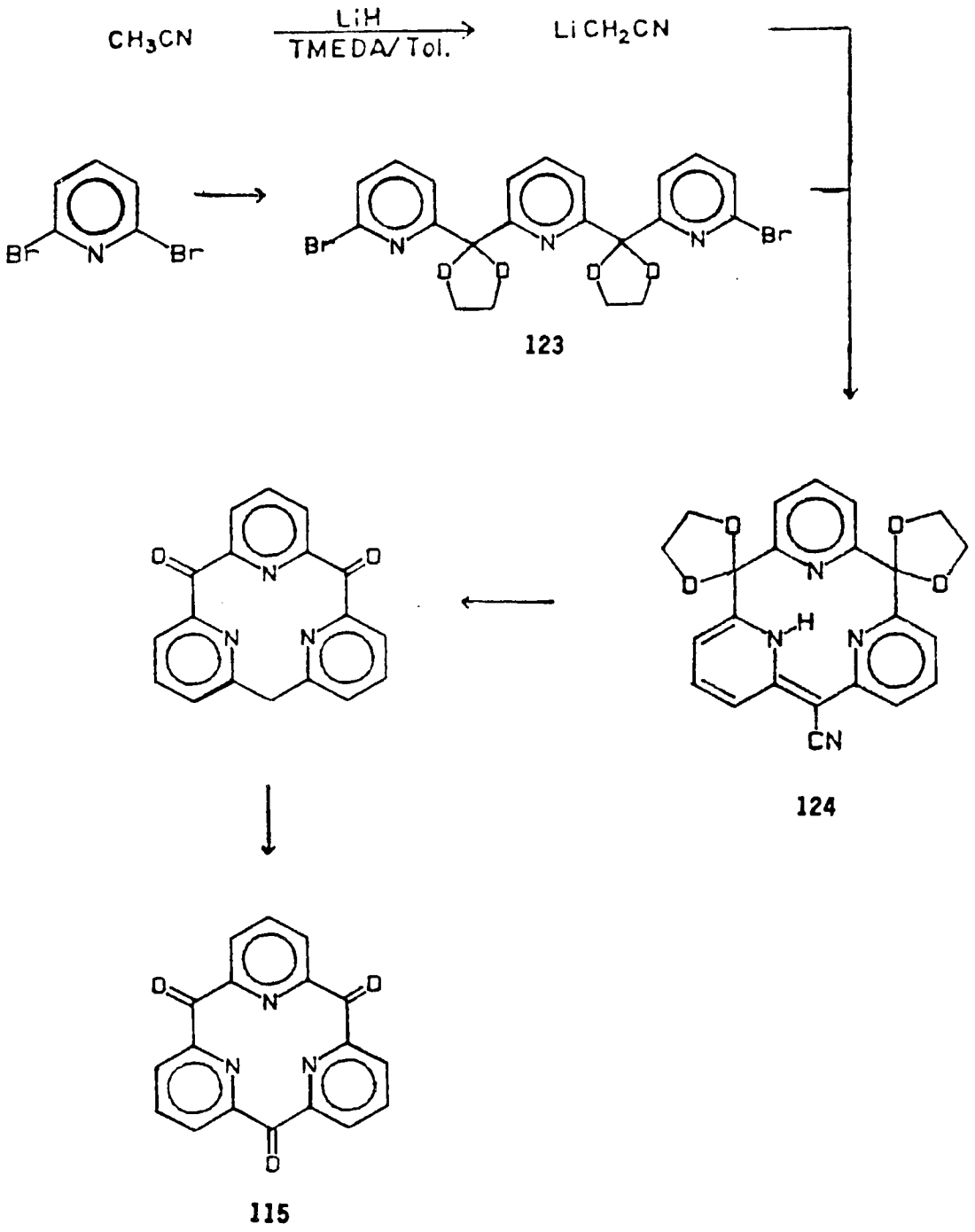


121



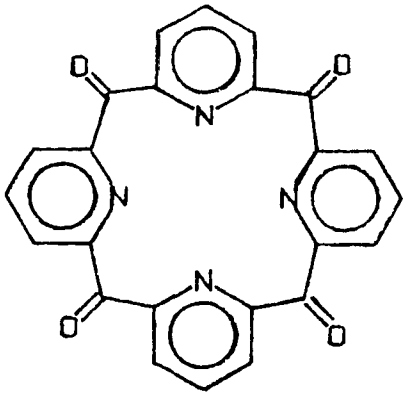
122

Scheme 4.


CH3CN
LiH
TMEDA/Tol.
LiCH2CN
Br
N
Br
Br
N
N
N
Br
O
O
O
O
123
O
N
O
N
N
N
H
N
CN
124
O
N
O
N
N
O
115

The initially attempted procedure was analogous to that employed in the synthesis of **121** and **122**, in which mono-α-lithiation of acetonitrile at 80°C and subsequent reaction with *bis*-ketal **123**[118,119] should produce **124**. Subsequent hydrolysis and oxidation of **124** should afford the desired triketone **115**.

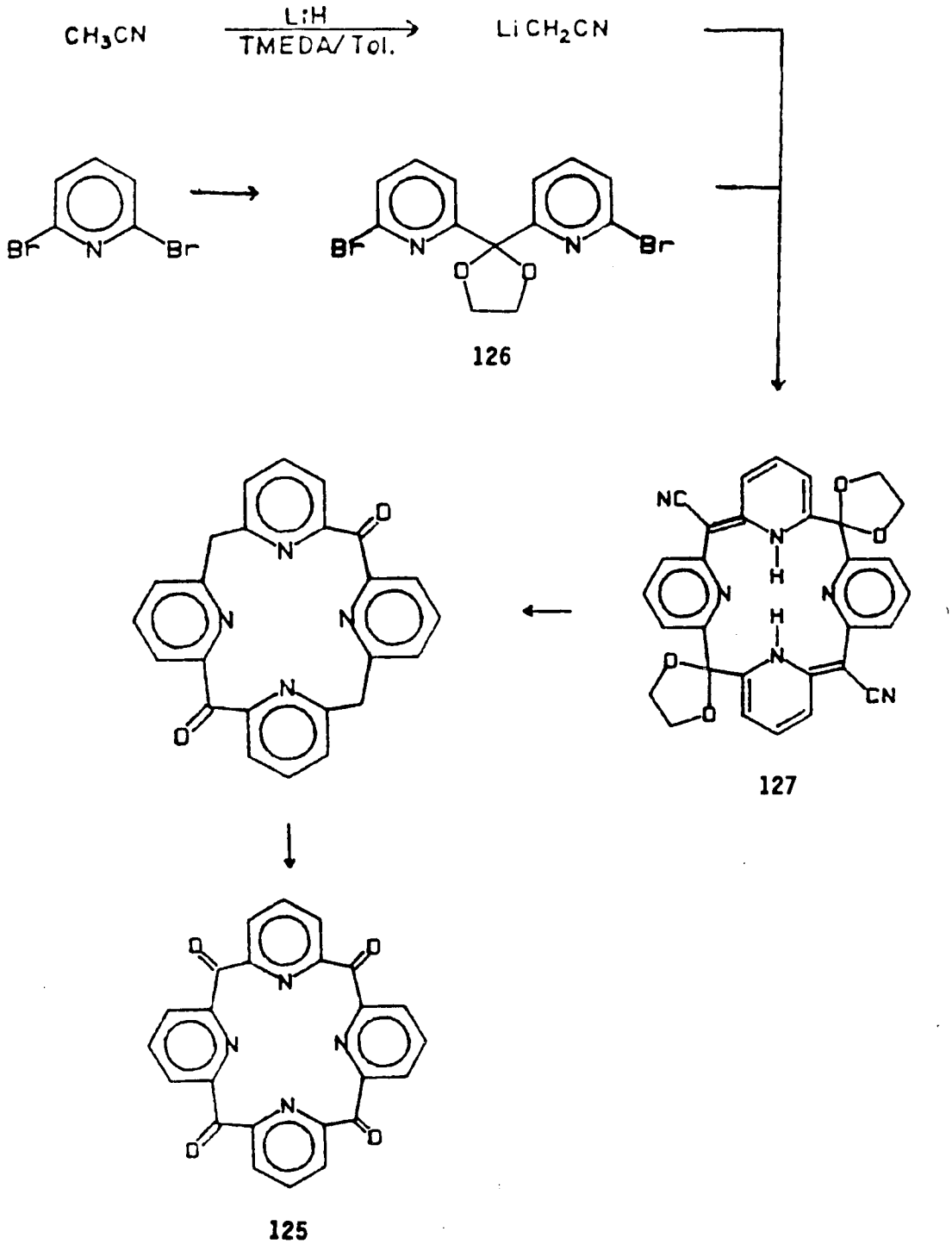
Tetraketone **125** possesses a 16-membered inner core analogous to the tetrapyrrolic derivative called "xanthoporphyrinogen". Numerous questions concerning the oxidation state of this "pyridyl"-porphyrin needed to be defined and considered in terms of planarity, ligand charge, comparable chromophoric π-electron localization (or distribution), redox potentials, spectral and physical data, pharmacological properties, electron-transport in membrane systems, and photochemical properties. These characteristics need to be evaluated in both porphyrins and metalloporphyrins.



125

The reaction between 2,2-*bis*-2′-(6′-bromopyridyl)-1,3-dioxolane (**126**), which was prepared from 2,6-dibromopyridine in two steps,[118,119] and the lithium salt of acetonitrile should give a

Scheme 5.



tetrapyridine macrocycle **127**, containing both ketal and nitrile bridging functionalities. Macrocycle **127** should be hydrolyzed and subsequently oxidized to give the desired tetraketone **125** (Scheme 5).

The chemistry and structural characteristics of the novel macromolecules will be the major topics of the dissertation. We can use these macromolecules to explore the chemistry of specifically designed nitrogen heteromacrocycles in order to ascertain their potential as biological models and to probe the actual size/shape (volume) of an *N*-electron pair within a cavity: for examples, (1) design new synthetic routes to pyridine-containing heteromacrocycles which possess a rigid non-flexible framework of known structural constraints which are similar to the porphyrin skeletal backbones; (2) determine the selective metal ion coordination and general ligand potential of these macrocycles; (3) study the unique electronic and structural relationships between these proposed macrocyclic models and known biological tetrapyrrole systems; (4) ascertain the possible substitution of non-metal bonded complexes for more intricate heme-containing proteins; and (5) elucidate the specific binding site properties as a factor in the action of mitochondrial electron-transfer, redox reactions, and semiconduction.

VI. Experimental

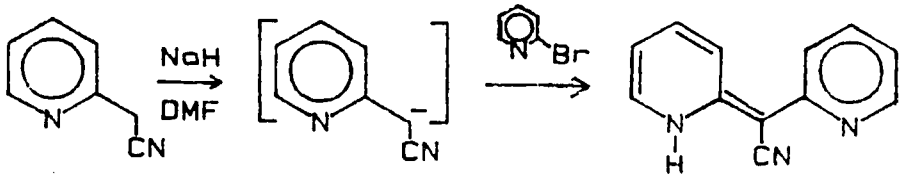
General Comments. Uncorrected melting points were measured in capillary tubes with a Thomas-Hoover Unimelt or Laboratory Devices MEL-TEMP apparatus for samples melting below or above 260°C, respectively. Infrared (IR) spectra were recorded with a Perkin-Elmer 621 Grating Spectrophotometer. ^{1}H NMR spectra were measured with a Bruker WP-80, AC-100, WP-200 or AM-400 Spectrometer in $CDCl_3$ solvent, except where noted, containing Me_4Si, as an internal standard. ^{13}C NMR spectra were recorded on a Bruker WP-80 Spectrometer operating at 20 MHz or a Bruker WP-200 Spectrometer operating at 50 MHz; the middle peak of $CDCl_3$ triplet was used as the reference. Mass spectra (MS) data were obtained by Mr. Herbert M. Land on a Hewlett-Packered Model 5985 GC/MS Spectrometer and are recorded herein as (assignment, relative intensity). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

The recorded R_f values were determined by a standard thin-layer chromatography (TLC) procedure: Baker-flex Silica-Gel IB2-F or Alumina IB2-F flexible sheets (7.5x2.5cm) were used without activation eluting with the stipulated solvent system. Preparative thick-layer chromatography (ThLC) was performed on 20x40cm glass plates coated with a 2mm layer of Brinkmann Silica Gel P/UV-254-366 or EM-Aluminum Oxide PF-254 Type T activated at 115°C for a minimum of four hours eluting with the stimulated solvent. Column chromatography was performed utilizing either silica gel (Baker,

60-200 mesh) or aluminium oxide (Brinkmann EM, neutral, Activity I, 70-230 mesh).

Unless otherwise indicated, all of the chemicals were reagent grade and no additional purification was deemed necessary. Benzene and toluene were distilled over sodium and stored over molecular sieves (Linda Type 4A). Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use. Acetonitrile was distilled[122] over P_2O_5 (0.5%-1.0%, w/v) after drying with molecular sieves (Linde Type 4A) and stored under N_2. *N,N*-Dimethylformaldehyde (DMF) and dimethylsulfoxide (DMSO) were distilled[123] from CaH_2 at reduced pressure and stored over molecular sieves (Linde Type 4A) under an argon atmosphere. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried over molecular sieves (Linde Type 4A), distilled from *n*-butyllithium (2.5N, *n*-hexane, 5% v/v) and stored under N_2.[124]

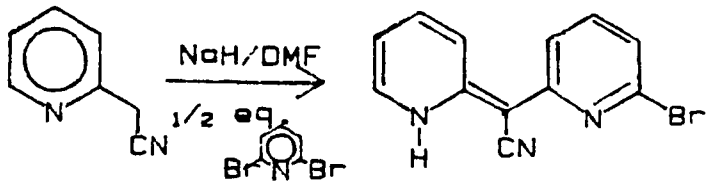
The X-ray data were collected on an Enraf-Nonius CAD4 diffractometer equipped with either MoKα (λ=0.71073Å) or CuKα (λ=1.54184Å) radiation and a graphite monochromator. Crystallographic calculations were conducted with the programs MULTAN and the Enraf-Nonius Structural Determination Package on a Digital Equipment PDP 11/34 or micro VAX II computer.



128

1. Bis(2-pyridyl)acetonitrile (128). A General Method.

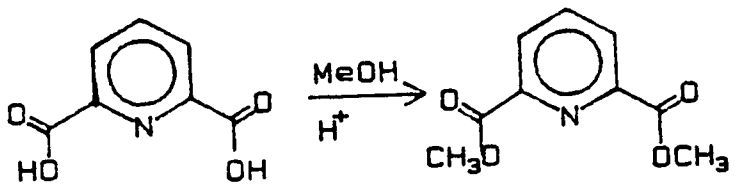
Oil-free NaH (980mg, 41mmol) was added to a stirred solution of 2-cyanomethylpyridine[92a] (1.21g, 10.3mmol) in dry DMF (100mL) at 25°C under a N_2 atmosphere. Upon addition of NaH, the pale yellow solution changed to an orange slurry, then after 30 min, 2-bromopyridine (1.62g, 10.3mmol) was added at 25°C. The resultant dark brown slurry was heated to 90°C for 6 h, after which the reaction was cooled to 25°C and quenched with water. The mixture was concentrated *in vacuo*, made acidic with 0.1N HCl, and extracted with $CHCl_3$ (2x100mL). The combined organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting yellow solid was column chromatographed (silica gel, DCM) and recrystallized from $CHCl_3$/benzene to afford (73%) *bis*(2-pyridyl)acetonitrile (128), as yellow fibers: 1.45g; mp 129-130°C (lit.[112] mp 129°C); R_f 0.34 (silica gel, DCM); ^1H NMR δ6.61 (td, 5-py*H*, J=5.9, 2.1Hz, 2H), 7.44 (m, 3,4-py*H*, 4H), 7.91 (dt, 6-py*H*, J=5.7, 1.3Hz, 2H), 16.3 (bs, N*H*, 1H); ^{13}C NMR δ67.5 (*C*C≡N), 112.5 (*C*5), 119.3 (*C*3), 122.0 (*C*≡N), 136.2 (*C*4), 139.1 (*C*6), 155.1 (*C*2); IR (KBr) 2190 cm^{-1} (C≡N); MS m/e 196 (M^++1, 8), 195 (M^+, 75), 194 (M^+-H, 100), 169 (M^+-CN, 64).



129

2. 2-Pyridyl-2′-(6′-bromopyridyl)acetonitrile (129).

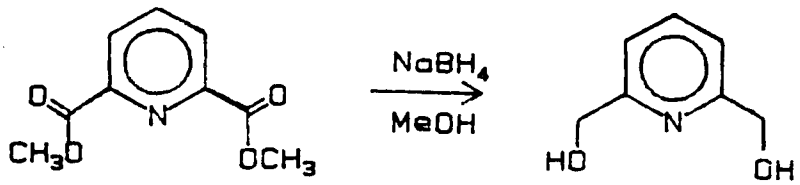
A mixture of 2-cyanomethylpyridine (490mg, 4.2mmol), oil-free NaH (400mg, 16.6mmol), 2,6-dibromopyridine (490mg, 2.1mmol), and dry DMF (100mL) was heated to 120°C for 16 h under a N_2 atmosphere. After cooling to 25°C, the mixture was quenched with water, concentrated *in vacuo*, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from $CHCl_3$/*n*-hexane to afford (81% from 2,6-dibromopyridine) **129**, as yellow fibers: 460mg; mp 157-158°C; R_f 0.39 (silica gel, DCM); ^1H NMR δ6.49 (m, 5-py*H*, 1H), 6.97 (dd, 5′-py*H*, J=5.0, 2.2Hz, 1H), 7.37 (m, 3,4,3′,4′-py*H*, 4H), 7.6 (m, 6-py*H*, 1H), 15.1 (bs, N*H*, 1H); ^{13}C NMR δ68.4 (*C*C≡N), 110.5 (*C*5), 117.3 (*C*5′), 119.1 (*C*3), 121.3 (*C*≡N), 133.4 (*C*3′), 137.4 & 137.6 (*C*4,4′), 138.4 (*C*6), 138.6 (*C*6′), 152.7 (*C*2′), 158.5 (*C*2′); IR (KBr) 2185cm^{-1} (C≡N); MS m/e 275 [M^+(^{81}Br), 80], 274 [M^+(^{81}Br)-H, 76], 273 [M^+(^{79}Br), 100], 272 [M^+(^{79}Br)-H, 72], 249 [M^+(^{81}Br)-CN, 63], 247 [M^+(^{79}Br)-CN, 66], 194 (M^+-Br, 37), 193 (M^+-HBr, 42), 167 (M^+-CHNBr, 26); Anal. Calcd. for $C_{12}H_8BrN_3$: C, 52.58; H, 2.94; N, 15.33. Found: C, 52.65; H, 3.11; N, 15.66.



130

3. Dimethyl 2,6-Pyridinedicarboxylate (130).

Concentrated HCl (5mL) was added to a solution of 2,6-pyridinedicarboxylic acid (68.27g, 409mmol) in MeOH (500mL) and refluxed for 10 h. Excess MeOH was evaporated *in vacuo* and the white residue was dissolved in $CHCl_3$, washed sequentially with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford (90%) dimethyl 2,6-pyridinedicarboxylate (130): 71.57g; mp 122-124°C (lit.[117] mp 124-125°C); ^1H NMR δ4.00 (s, CH_3, 6H), 8.04 (t, 4-py*H*, J=7.6Hz, 1H), 8.32 (d, 3,5-py*H*, J=7.6Hz, 2H).

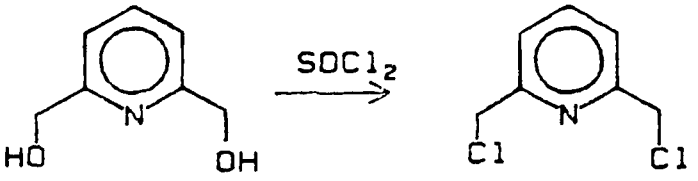


130 131

4. 2,6-*Bis*(hydroxymethyl)pyridine (131).

To a stirred solution of **130** (38.0g, 0.20mol) in absolute MeOH (300mL), $NaBH_4$ (38g, 1.0mol) was added slowly *via* a solid addition funnel. The temperature was maintained at 45±5°C with intermittent

ice bath cooling. After the addition was completed, additional MeOH (50mL) was introduced and the mixture was warmed for 2.5 h to 45±5°C, after which acetone (100mL) was added. The organic solvent was evaporated *in vacuo*, then water was added to the residue. Diol **131** was extracted with $CHCl_3$ for 2 days with a continuous liquid-liquid extractor, after concentration of the eluent, the solid was recrystallized from *p*-xylene to give (80%) **131**, as colorless needles: 21.6g; mp 112-113°C (lit.[119] mp 111-112°C); ^1H NMR (DMSO-d_6) δ4.13 (s, CH_2, 4H), 4.59 (s, O*H*, 2H), 7.34 (d, 3,5-py*H*, J=7.7Hz, 2H), 7.81 (t, 4-py*H*, J=7.7Hz, 1H).

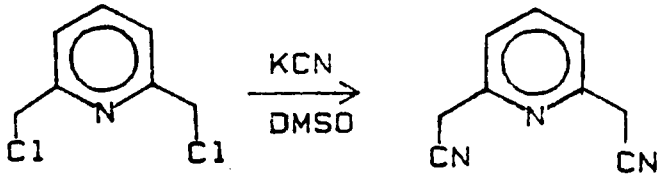


131 **132**

5. 2,6-*Bis*(chloromethyl)pyridine (132).

Diol **131** (13.0g, 94mmol) was added slowly to redistilled[123] $SOCl_2$ (10mL) at 0°C under a N_2 atmosphere and then mixture was refluxed for 2 h. The excess $SOCl_2$ was removed *in vacuo* to give a residue, which was dissolved in $CHCl_3$, washed with aqueous saturated $NaHCO_3$, and then aqueous saturated NaCl. The combined $CHCl_3$ extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a solid, which was column chromatographed (silica gel, DCM). Further purification was achieved by recrystallization from light petroleum ether to give (77%) **132**, as colorless needles:

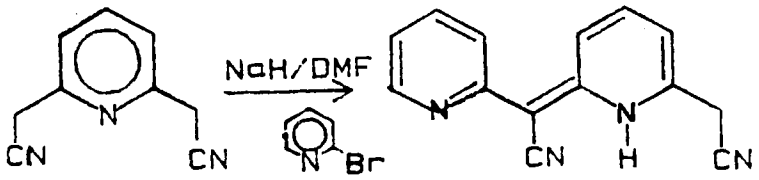
12.7g; mp 71-73°C (lit.[92a] mp 74-75°C; ^{1}H NMR δ4.65 (s, C*H*$_2$, 4H), 7.40 (d, 3,5-py*H*, J=4.5Hz, 2H), 7.77 (t, 4-py*H*, J=8.0Hz, 1H).



132 *133*

6. 2,6-*Bis*(cyanomethyl)pyridine (133).

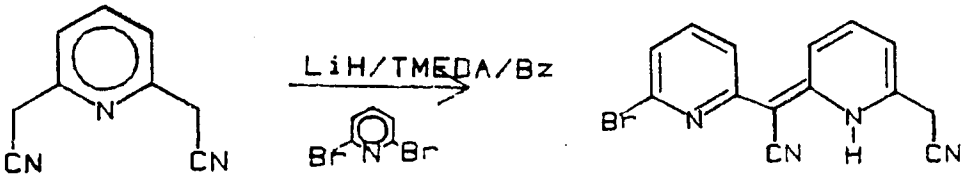
A solution of 132 (9.9g, 56mmol) in dry DMSO (100mL) was added dropwise over 2 h to a stirred solution of KCN (22g, 340mmol) in dry DMSO (100mL) under a N_2 atmosphere at 35±5°C. After 26 h, the mixture was poured into a solution of aqueous saturated Na_2CO_3 (500mL) containing aqueous NaOH (40%, 10mL) and extracted sequentially with Et_2O and $CHCl_3$. The combined organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was suspended in $CHCl_3$ and filtered through a short column of silica gel. The filtrate was evaporated and the residue recrystallized from EtOH to afford (55%) 133, as colorless needles: 4.9g; mp 96-98°C (lit.[92a] mp 97-98°C); ^{1}H NMR δ3.92 (s, C*H*$_2$C≡N, 4H), 7.41 (d, 3,5-py*H*, J=7.8Hz, 2H), 7.80 (t, 4-py*H*, J=7.8Hz, 1H).



133 134

7. 2-Pyridyl-2′-(6′-cyanomethylpyridyl)acetonitrile (134).

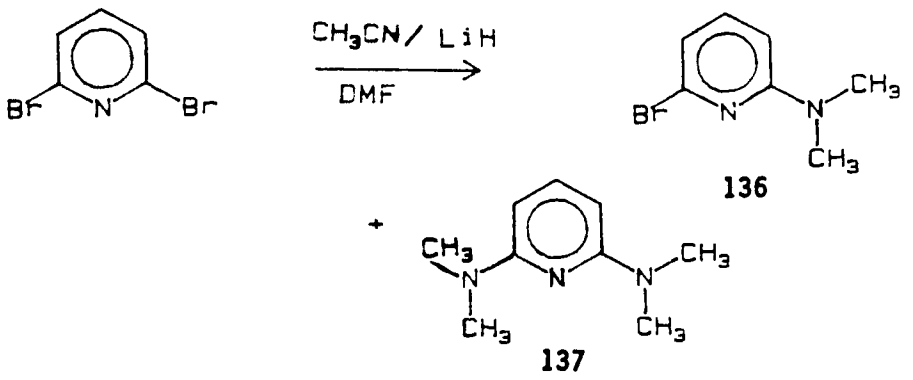
Oil-free NaH (570mg, 24mmol) was added to a solution of 133 (470mg, 3.0mmol) in dry DMF (100mL) under a N_2 atmosphere at 25°C. Upon addition of NaH, the color changed from yellow to brown. 2-Bromopyridine (950mg, 6.0mmol) was added to this brown suspension, then heated to 90±5°C for 7 h. After cooling, the mixture was quenched with water, concentrated *in vacuo*, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from DCM/*n*-hexane to afford (34%) 134, as yellow needles: 250mg; mp 246-248°C; R_f 0.25 (silica gel, DCM); ^1H NMR δ4.00 (s, $CH_2C{\equiv}N$, 2H), 6.73 (m, 5-py*H*, 1H), 7.60 (m, 3,4,-3′,4′,5′-py*H*, 5H), 8.63 (d, 6-py*H*, J=4.0Hz, 1H), 15.8 (bs, N*H*, 1H); ^{13}C NMR δ27.2 (CH_2), 75.5 ($CC{\equiv}N$), 111.1 (*C*5′), 114.2 (*C*5), 118.6 (*C*3′), 121.6 (*C*3), 122.7 & 123.3 ($C{\equiv}N$), 134.9 (*C*4′), 137.9 & 138.1 (*C*4,6), 146.7 (*C*6′), 153.7 & 154.3 (*C*2,2′); IR (KBr) 2250, 2180cm^{-1} (C≡N); MS m/e 235 (M^++1, 17), 234 (M^+, 100), 233 (M^+-H, 80), 208 (M^+-CN, 58), 207 (M^+-CHN, 21); Anal. Calcd. for $C_{14}H_{10}N_4 \cdot 1/4H_2O$: C, 70.42; H, 4.43; N, 23.47. Found: C, 69.80; H, 4.75; N, 23.57.



133 135

8. 2-(6-Bromopyridyl)-2'-(6'-cyanomethylpyridyl)acetonitrile (135).

A mixture of LiH (250mg), 2,6-dicyanomethylpyridine (133; 420mg, 2.7mmol), and 2,6-dibromopyridine (630mg, 2.7mmol) in dry TMEDA (5mL) and dry benzene (95mL) was refluxed for 2 days under a N_2 atmosphere. The resulting yellow mixture was quenched with water and concentrated *in vacuo*. The yellow solid was dissolved in DCM, which was washed with aqueous saturated $NaHCO_3$ and dried over anhydrous $MgSO_4$. Evaporation of the extract *in vacuo* gave a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from DCM/*n*-hexane to give (75%) pure **135**, as yellow fibers: 640mg; mp 255-257°C; R_f 0.76 (silica gel, 10% EtOH/DCM); ^1H NMR δ5.41 (d, C*H*$_2$, J=2.0Hz, 2H), 6.72 (dt, 5'-py*H*, J=6.3, 2.0Hz, 2H), 6.96 (dd, 3'-py*H*, J=6.1, 2.3Hz, 2H), 7.26-7.73 (m, 3,4,5,4'-py*H*, 4H), 15.6 (bs, N*H*, 1H); IR (KBr) 2245, 2190cm^{-1} (C≡N); MS m/e 314 [$M^+(^{81}Br)$, 95], 313 [$M^+(^{81}Br)$-H, 55], 312 [$M^+(^{79}Br)$, 100], 288 [$M^+(^{81}Br)$-CN, 89], 286 [$M^+(^{79}Br)$-CN, 90], 274 [$M^+(^{81}Br)$-C_2H_2N, 27], 272 [$M^+(^{79}Br)$-C_2H_2N, 28], 232 (M^+-HBr, 20); Anal. Calcd. for $C_{14}H_9BrN_4 \cdot H_2O$; C, 50.77; H, 3.34; N, 13.92. Found: C, 50.91; H, 2.90; N, 14.03.



136

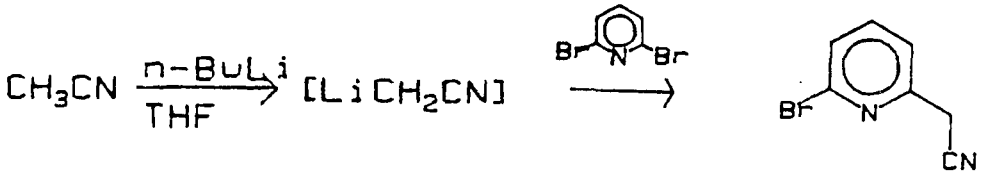
137

9. 6-Bromo-2-(dimethylamino)pyridine (136) and 2,6-*bis*(dimethylamino)pyridine (137).

A mixture of 2,6-dibromopyridine (3.44g, 14.5mmol), oil-free LiH (610mg, 76mmol), MeCN (310mg, 7.6mmol), and dry DMF (50mL) was heated to 120°C for 24 h under a N_2 atmosphere. After cooling to 25°C, the mixture was quenched with water, concentrated *in vacuo*, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a dark brown oil, which was chromatographed (silica gel, DCM) to afford two major products:

Fraction A was recrystallized from C_6H_{12} to give (35%) 6-bromo-2-(dimethylamino)pyridine (136), as colorless microcrystals: 1.02g; mp 56-57°C; R_f 0.71 (silica gel, DCM); ^1H NMR δ3.05 (s, C*H*$_3$, 6H), 6.35 (dd, 3-py*H*, J=8.4, 0.5Hz, 1H), 6.65 (dd, 5-py*H*, J=7.0, 0.5Hz, 1H), 7.23 (dd, 4-py*H*, J=8.4, 7.5Hz, 1H); MS m/e 202 [$M^+(^{81}Br)$, 58], 200 [$M^+(^{79}Br)$, 59], 187 [$M^+(^{81}Br)-CH_3$, 48], 185 [$M^+(^{79}Br)-CH_3$, 43], 173 [$M^+(^{81}Br)-C_2H_5$, 93], 171 [$M^+(^{79}Br)-C_2H_5$, 100]; Anal. Calcd. for $C_7H_9BrN_2 \cdot 1/4C_6H_{12}$: C, 45.96; H, 5.45; N, 10.62. Found; C, 46.49; H, 5.17; N, 10.87.

Fraction B was recrystallized from C_6H_{12} to afford (15%) 2,6-*bis*(dimethylamino)pyridine (137), as a colorless solid: 360mg; mp 31-32° (lit.[125] mp 33-34°C); R_f 0.33 (silica gel, DCM); ^{1}H NMR δ3.02 (s, C*H*$_3$, 12H), 5.80 (d, 3-py*H*, J=8.0Hz, 2H), 7.27 (t, 4-py*H*, 8.0Hz, 1H); MS m/e 166 (M^++1, 26), 165 (M^+, 100), 150 (M^+-CH_3, 46), 136 (M^+-C_2H_5, 69), 121 (M^+-C_3H_8, 31).

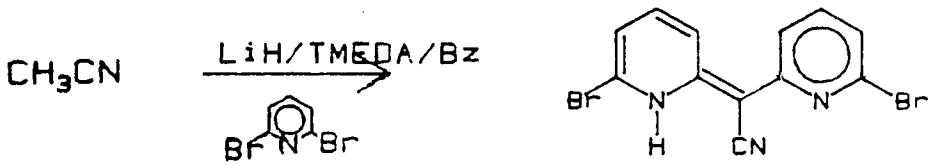


138

10. 2-(6-Bromopyridyl)acetonitrile (138).

To a stirred solution of *n*-butyllithium (1.6N/*n*-hexane; 4.3mL, 6.9mmol) at -70°C under a N_2 atmosphere, was rapidly added dry THF (50mL), followed immediately by a solution of dry MeCN (400μL, 320mg, 7.7mmol) in dry THF (20mL) added over a 5 min period. After one h at below -70°C, the resulting white suspension was treated with 2,6-dibromopyridine (540mg, 2.3mmol). The pale yellow solution was stirred for one h at -70°C and then warmed to 25°C before quenching with water. The organic solvent was evaporated *in vacuo* to give a yellowish solid, which was dissolved in DCM. The organic layer was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$ to give the crude product, which was recrystallized from *n*-hexane to afford (27%) 138, as white needles: 120mg; mp 43.0-43.5°C; R_f 0.46 (silica gel, DCM); ^{1}H NMR δ3.93 (s, C*H*$_2$, 2H),

7.42 (m, 3,5-py*H*, 2H), 7.63 (t, 4-py*H*, J=7.0Hz, 1H); ^{13}C NMR δ22.6 (*C*H_2), 121.0 (*C*3), 122.8 (*C*≡N), 127.6 (*C*5), 130.9 (*C*2), 139.6 (*C*4), 142.2 (*C*6); MS m/e 198 [M^+(^{81}Br), 52], 196 [M^+(^{79}Br), 48], 117 [M^+-Br, 100), 90 (M^+-CNBr, 64); Anal. Calcd. for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: 42.47; H, 2.54; N,13.74.

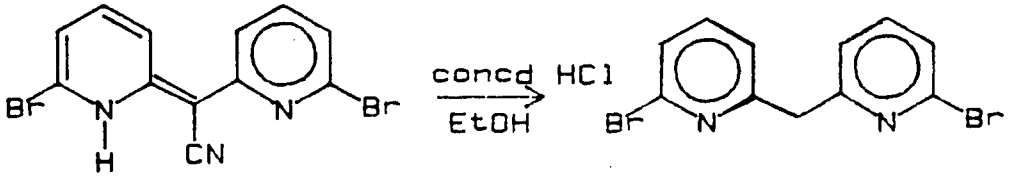


122

11. *Bis*-2-(6-bromopyridyl)acetonitrile (122). A General Procedure.

To a stirred mixture of LiH (1.0g, 125mmol) in dry TMEDA (10mL) and dry toluene (250mL) at 25°C under a N_2 atmosphere, was added dry MeCN (1.1mL, 860mg, 21mmol). The resulting white suspension was treated with 2,6-dibromopyridine (5.04g, 21mmol) and the pale yellow suspension was refluxed for 2 days, then poured onto ice-water (200mL) containing concentrated HCl (10mL). The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. The organic solvent was then evaporated *in vacuo* to give a yellow solid, which was column chromatographed (alumina, DCM) and recrystallized from DCM/ cyclohexane to give (47%) 122, as yellow fibers: 1.77g; mp 163-164°C; R_f 0.40 (silica gel, DCM); ^{1}H NMR δ6.61 (m, 5-py*H*, 2H), 7.51 (m, 3,4-py*H*, 4H), 16.0 (bs, N*H*, 1H); ^{13}C NMR δ64.5 (*C*C≡N), 116.2

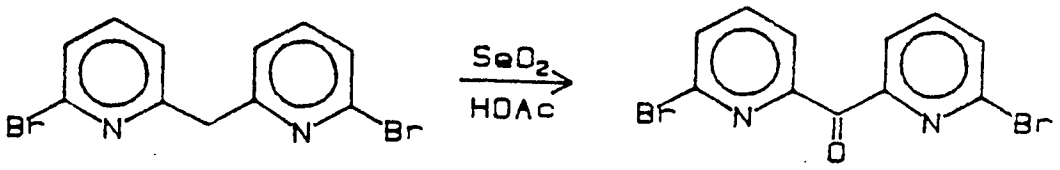
(*C*5), 118.5 (*C*3), 121.8 (*C*≡N), 128.2 (*C*4), 138.2 (*C*6), 141.6 (*C*2); IR (KBr) 2200cm^{-1} (C≡N); MS m/e 355 [M$^+$($^{2}{}^{81}$Br), 45], 354 [M$^+$($^{2}{}^{81}$Br)-H, 35], 353 [M$^+$(^{81}Br^{79}Br), 100], 352 [M$^+$(^{81}Br^{79}Br)-H, 53], 351 [M$^+$($^{2}{}^{79}$Br), 54], 329 [M$^+$($^{2}{}^{81}$Br)-CN, 40], 327 [M$^+$(^{81}Br^{79}Br)-CN, 85], 325 [M$^+$($^{2}{}^{79}$Br)-CN, 40]; Anal. Calcd. for $C_{12}H_7Br_2N_3$: C, 40.83; H, 2.00; N, 11.90. Found: C, 41.16; H, 2.11; N, 11.92.



122 139

12. *Bis*-2-(6-bromopyridyl)methane (139).

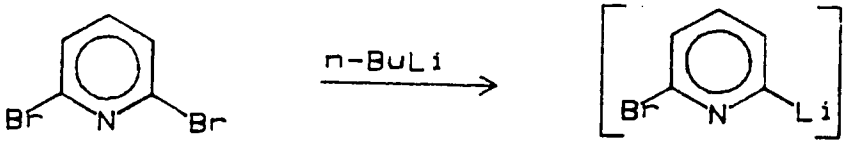
A mixture of 122 (740mg, 2.1mmol) in concentrated HCl (50mL) and EtOH (50mL) was refluxed for 8 h. The resulting colorless solution was carefully neutralized with NaOH (15g) and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to afford (81%) crude 139, which was quite susceptible to air oxidation: 560mg; R_f 0.20 (silica gel, DCM); ^{1}H NMR δ4.27 (s, CH_2, 2H), 7.19 (m, 3-py*H*, 2H), 7.37 (dd, 5-py*H*, J=9.0, 3.2Hz, 2H), 7.58 (t, 4-py*H*, J=7.7Hz, 2H). 139 was not purified further but immediately oxidized to 140.



139 140

13. *Bis*-2-(6-bromopyridyl)ketone (140).

A mixture of **139** (240mg, 0.73mmol), SeO_2 (280mg) in glacial AcOH (20mL) was refluxed for 22 h. The mixture was filtered through a Celite pad and concentrated *in vacuo* to dryness, then the residue was dissolved in $CHCl_3$. Organic layer was washed aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, and dried over anhydrous $MgSO_4$ to yield (72% from **122**) **140**: 180mg; mp 151-153°C (lit.[121a] mp 155-156.5°C); ^1H NMR δ7.70 (d, 5-py*H*, J=2.6Hz, 2H), 7.72 (d, 3-py*H*, J=6.0Hz, 2H), 8.08 (dd, 4-py*H*, J=6.0, 2.6Hz, 2H).

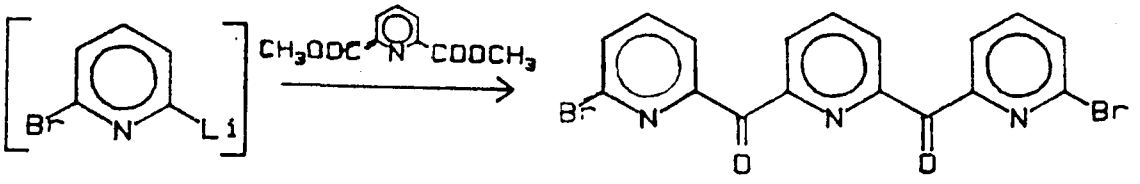


141

14. 6-Bromo-2-lithiopyridine (141). A General Method.[121a]

A stirred solution of 2,6-dibromopyridine (19.1g, 80.4mmol) in anhydrous Et_2O (400mL) was cooled to -70°C (Dry ice/acetone bath) under a N_2 atmosphere, to which was added *n*-BuLi (33mL, 84mmol; 2.5M/ *n*-hexane) at such a rate that the temperature did not exceed

-60°C. The clear, golden yellow solution was maintained below -70°C for 30 min, prior to addition of the electrophile. In following experiments, the amounts of **141** listed refer to the starting 2,6-dibromopyridine.

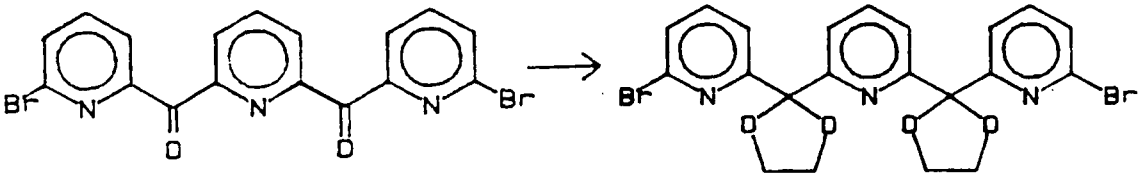


141 **142**

15. 2,6-*Bis*[2'-(6'-bromopicolinoyl)]pyridine (142).

A solution of 2-bromo-6-lithiopyridine (**141**) [prepared from 2,6-dibromopyridine (22.23g, 93.8mmol) and *n*-BuLi (65mL, 103mmol; 1.6N/*n*-hexane)] in anhydrous Et_2O (350mL) was cooled to -70°C. Solid dimethyl 2,6-pyridinedicarboxylate (**130**; 9.15g, 46.9mmol) was added with vigorous stirring. The solution was maintained at -70°C for one h, followed by thirty min at -40°C. The mixture was hydrolyzed with MeOH (50mL), concentrated HCl (20mL), and water (100mL), respectively, then the ethereal solvent was removed *in vacuo*. The acidic aqueous suspension was refluxed for ten h, cooled, then neutralized (carefully) with saturated Na_2CO_3 and extracted with DCM. The extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a brown, pasty mass, which was triturated with boiling Et_2O (6x20mL); the residue was recrystallized from benzene to afford (36%) the diketone **142**: 7.46g; mp 138-140°C (lit.[121c] mp 142-143°C); ^1H NMR δ7.48 (dd,

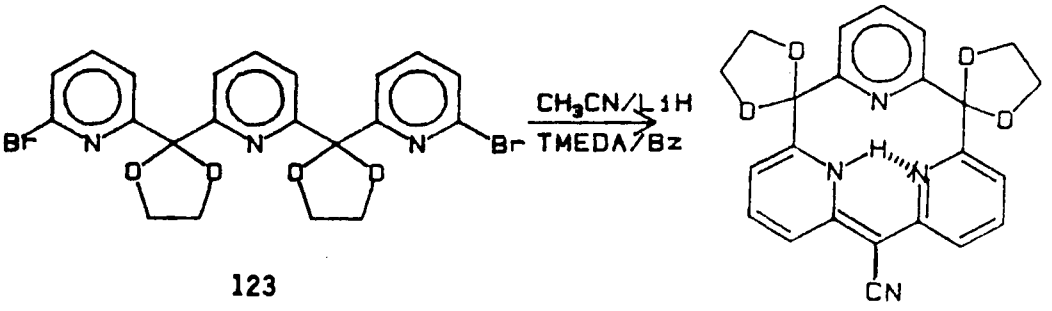
5′-py*H*, J=7.5, 1.0Hz, 2H), 7.82 (t, 4′-py*H*, J=7.6Hz, 2H), 8.04-8.21 (m, 3′,4-py*H*, 4H), 8.36 (d, 3-py*H*, J=7.7Hz, 2H); MS m/e 449 [$M^+(2^{81}Br)$, 8], 447 [$M^+(^{81}Br^{79}Br)$, 17], 445 [$M^+(2^{79}Br)$, 8], 392 [$M^+(2^{81}Br)-C_2O_2$, 6], 390 [$M^+(^{81}Br^{79}Br)-C_2O_2$, 11], 388 [$M^+(2^{79}Br)-C_2O_2$, 5], 312 [$M^+(^{81}Br)-C_2O_2Br$, 21], 310 [$M^+(^{79}Br)-C_2O_2Br$, 20], 263 [$M^+(^{81}Br)-C_6H_3OBr$, 100], 261 [$M^+(^{79}Br)-C_6H_3OBr$, 91].



142 123

16. 2,6-*Bis*[2′-(6′-bromopyridyl)-1,3-dioxolan-2-yl]pyridine (123).

A mixture of diketone 142 (11.1g, 25mmol), freshly distilled ethylene glycol (50mL), and concentrated H_2SO_4 (10 drops, 0.5mL) in dry toluene (400mL) was refluxed gently for 10 days. Water was removed with a Dean-Stark water separator. After cooling, the solution was concentrated *in vacuo* and the residue was slurried in aqueous saturated $NaHCO_3$, extracted with $CHCl_3$, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting buff solid was recrystallized from $CHCl_3$/EtOH to give (70%) diketal 123, as colorless, massive crystals: 9.3g; mp 186-188°C (lit.[121d] mp 189-190°C); ^1H NMR δ4.10 (s, CH_2, 8H), 7.32-7.56 (m, 3′,4′,5′-py*H*, 6H), 7.66-7.74 (m, 3,4-py*H*, 3H).



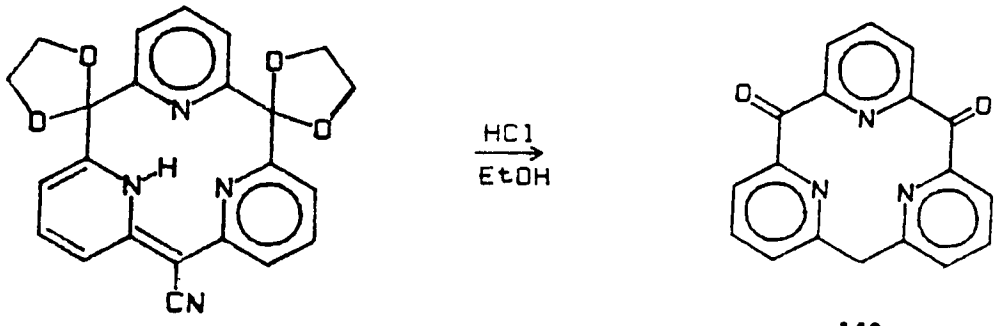
123

124

17. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1-cyano-5,9-dione Ethylene Glycol Bisketal (124).

To a stirred mixture of LiH (550mg) in dry TMEDA (10mL) and dry benzene (250mL) at 25°C under a N_2 atmosphere, was added dry MeCN (1.1mL). The resulting white suspension was treated with diketal 123 (1.98g, 3.7mmol), then the pale yellow suspension was refluxed for 3 days before it was poured into ice-water-HCl. The layers were separated and the aqueous layer was extracted with $CHCl_3$. Organic layer was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. After concentration, the yellow residue was column chromatographed (alumina, DCM), then recrystallized from DCM/C_6H_{12} to give (43%) tricyclopyridine 124, as yellow needles: 660mg; mp 268–269°C; R_f 0.34 (alumina, DCM); ^1H NMR δ4.26 (m, C*H*$_2$, 8H), 7.00 (m, 3-py*H*, 2H), 7.52 (m, 2,4,5-py*H*, 7H), 16.5 (bs, N*H*, 1H); ^{13}C NMR δ65.9 (*C*H$_2$), 69.0 (*C*C≡N), 104.9 (OCO), 109.7 (*C*3′), 119.4 & 119.6 (*C*3,5′), 122.6 (*C*≡N), 136.6 (*C*4′), 138.9 (*C*4), 150.7 (*C*2′), 154.4 (*C*6′), 157.4 (*C*2); IR (KBr) 2162cm^{-1} (C≡N); MS m/e 415 (M^++1, 31), 414 (M^+, 100), 370

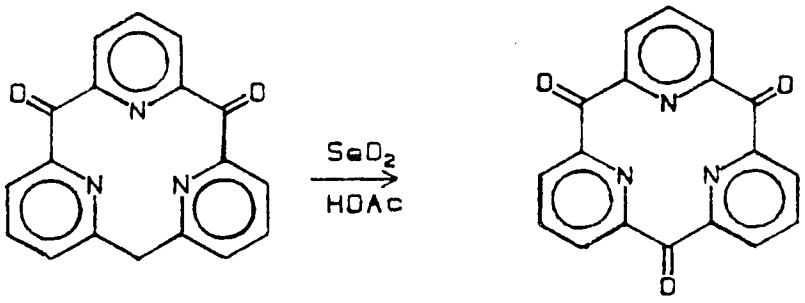
(M^+-C_2H_4O, 10), 326 (M^+-$C_4H_8O_2$, 28); Anal. Calcd. for $C_{23}H_{18}O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.36; H, 4.09; N, 13.25.



124 143

18. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5-dione (143).

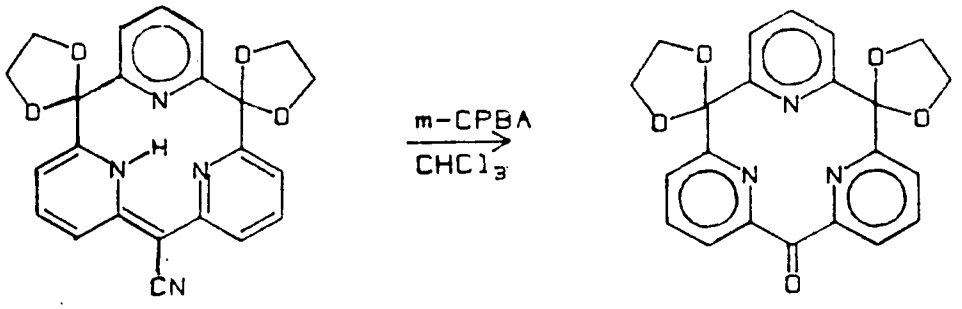
A mixture of 124 (720mg, 1.7mmol) in concentrated HCl (25mL) and EtOH (25mL) was refluxed for 5 h. Then the resulting colorless solution was cooled to 0°C and neutralized with solid NaOH and extracted with $CHCl_3$. The combined extract was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. After concentration, the resulting solid was recrystallized from DCM/EtOH to afford crude diketone **143**, which was unstable (easily oxidized): ^{1}H NMR δ4.40 (s, C*H*$_2$, 2H), 6.99-8.41 (m, py*H*, 9H); MS m/e 302 (M^++1, 21), 301 (M^+, 100), 272 (M^+-CHO, 27), 244 (M^+-C_2HO_2, 56), 217 (M^+-C_3O_3, 28). This dione was not purified further but immediately oxidized to **115**.



143 115

19. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione or 1,3,5-Tri-[2,6]pyridacyclohexaphane-2,4,6-trione (115).

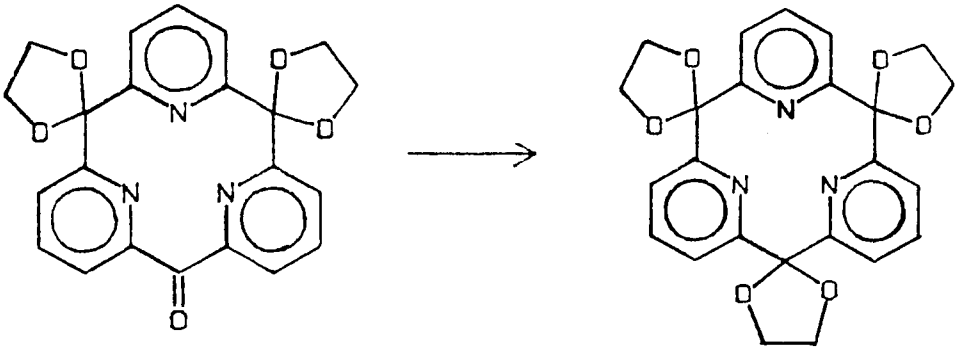
A mixture of crude diketone **143** (680mg, 2.3mmol) in glacial AcOH (50mL) and SeO_2 (800mg) was refluxed for 8 h. After additional SeO_2 (400mg) was added, the mixture was refluxed for an additional 8 h. Removal of AcOH *in vacuo*, following the filtration of Se° on Celite gave the colorless triketone **115**, which was column chromatographed on silica gel eluting from $CHCl_3$ to EtOH. The eluent was washed with aqueous saturated NaCl, and evaporated *in vacuo* to afford crude triketone **115**. Further purification by recrystallization from $CHCl_3$/EtOH gave (65% from **124**) **115**, as colorless needles: 350mg; mp 236.0-236.5°C; ^{1}H NMR δ8.12 (dd, 4-py*H*, $J_{3,4}=J_{4,5}$=7.9Hz, 3H), 8.34 (d, 3,5-py*H*, J=7.9Hz, 6H); ^{13}C NMR δ126.7 (*C*3), 138.0 (*C*4), 152.9 (*C*2), 188.1 (*C*=O); IR (KBr) 1667cm^{-1} (C=O); MS m/e 316 (M^++1, 21), 315 (M^+, 100), 287 (M^+-CO, 5), 258 ($M^+-C_2HO_2$, 8), 230 ($M^+-C_3HO_3$, 42); UV (CH_3CN) λ_{max}=227nm (log ϵ=4.43), 250 (sh, 4.32); (CH_3OH) 201 (4.43), 215 (sh, 4.36), 245 (sh, 4.11), 270 (sh, 4.04); Anal. Calcd. for $C_{18}H_9N_3O_3$: C, 68.57; H, 2.88; N, 13.33. Found: C, 68.17; H, 2.87; N, 13.11.



124 120

20. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione Ethylene Glycol Bisketal (120).

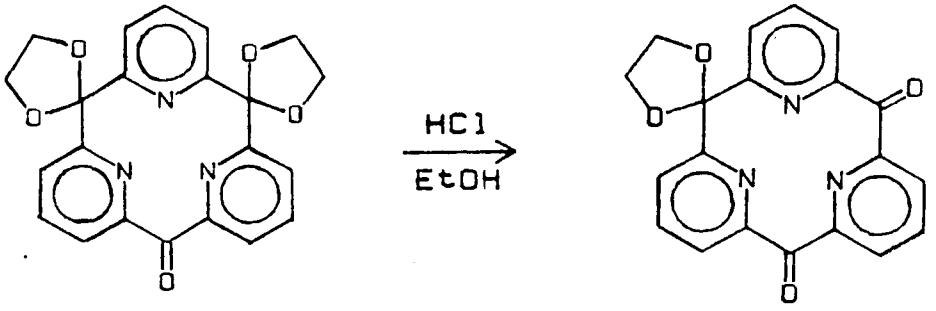
A stirred mixture of *m*-chloroperbenzoic acid (220mg, 85%, 1.0mmol) and 124 (380mg, 0.9mmol) in $CHCl_3$ (50mL) was maintained at 0°C for 5 h. The colorless solution was washed with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give diketalmonoketone 120, which was recrystallized (68%) from $CHCl_3$/EtOH: 250mg; mp 280°C (dec); R_f 0.21 (alumina, $CHCl_3$); ^{1}H NMR δ4.24 (s, CH_2, 8H), 7.47-7.95 (m, py*H*, 9H); ^{13}C NMR δ65.9 (CH_2), 107.7 (OCO), 119.4 (*C*3′), 122.2 (*C*5), 122.7 (*C*3), 136.2 (*C*4′), 136.6 (*C*4), 153.6 (*C*2′), 157.8 (*C*6), 158.1 (*C*2), 192.1 (*C*=O); MS m/e 404 (M^++1, 20), 403 (M^+, 83), 360 (M^+-C_2H_3O, 23), 332 (M^+-$C_3H_3O_2$, 63), 316 (M^+-$C_4H_7O_2$, 14), 288 (M^+-$C_6H_7O_4$, 100); Anal. Calcd. for $C_{22}H_{17}N_3O_5 \cdot 1/2H_2O$: C, 64.07; H, 4.40; N, 10.19. Found: C, 63.97; H, 4.34; N, 9.91.



120 144

21. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione Ethylene Glycol Triketal (144).

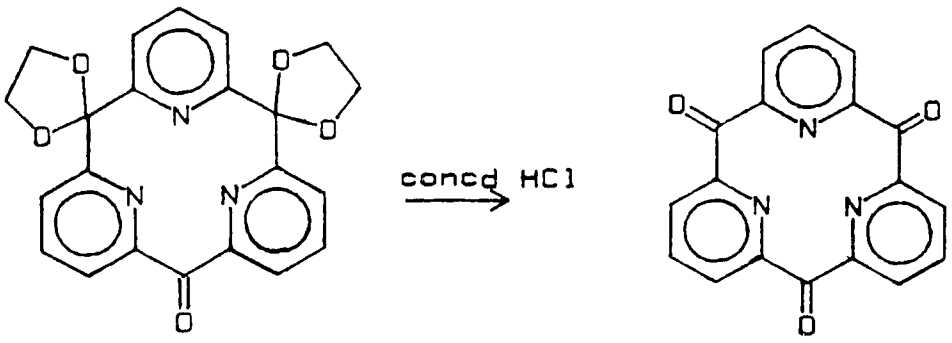
A toluene (50mL) solution of diketal **120** (110mg, 0.3mmol), freshly distilled ethylene glycol (2mL), and concentrated H_2SO_4 (3 drops, 0.1mL) was refluxed for 7 days, using a Dean-Stark water separator. The cooled solution was concentrated *in vacuo* and the residue was dissolved with $CHCl_3$ (300mL). The organic layer was washed with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the slightly yellow (crude) triketal **144**. Further purification of **144** was not successful because of low solubility: mp 280° (dec); ^{1}H NMR δ4.27 (s, C*H*$_2$, 12H), 7.71-7.93 (m, py*H*, 9H); MS m/e 448 (M^++1, 10), 447 (M^+, 39), 404 (M^+-$C_2H_3O_2$, 27), 360 (M^+-$C_4H_7O_4$, 13), 332 (M^+-$C_5H_7O_5$, 51).



120 119

22. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione Ethylene Glycol Monoketal (119).

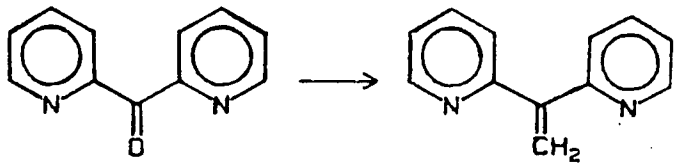
A mixture of diketal **120** (250mg, 0.6mmol) in concentrated HCl (5mL) and EtOH (50mL) was refluxed for 2 h. The resulting solution was carefully neutralized with aqueous saturated $NaHCO_3$ and then extracted with DCM (2x200mL). The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting colorless solid was recrystallized from $CHCl_3$/EtOH to give (54%) monoketal **119**, as colorless needles: 120mg; mp 235°C (dec); ^{1}H NMR δ4.30 (s, CH_2, 4H), 7.84-7.98 (m, 3′-5′-py*H*, 6H), 8.07 (t, 4-py*H*, J-7.5Hz, 1H), 8.28 (d, 3,5-pyH, J=7.5Hz, 2H); MS m/e 360 (M^++1, 9), 359 (M^+, 34), 288 (M^+-$C_3H_3O_2$, 100); Anal. Calcd. for $C_{20}H_{13}N_3O_4 \cdot H_2O$: C, 63.66; H, 4.01; N, 10.14. Found: C, 64.27; H, 4.07; N, 10.18.



120 115

23. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione (115).

A mixture of diketal **120** (110mg, 0.3mmol) in concentrated HCl (20mL) was refluxed for 36 h. Additional concentrated HCl (10mL) was added four times at 8 h intervals. The acidic solution was neutralized carefully with solid NaOH and then extracted with $CHCl_3$. The $CHCl_3$ extract was column chromatographed (silica gel, $CHCl_3$; EtOH; 10% HOAc/EtOH) and the eluent was washed with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, dried over anhydrous $MgSO_4$. Concentration of solvent *in vacuo* afforded crude triketone **115**. Further purification by recrystallization from $CHCl_3$/EtOH gave (60%) triketone **115** (52mg), which was identical to the previously prepared sample.



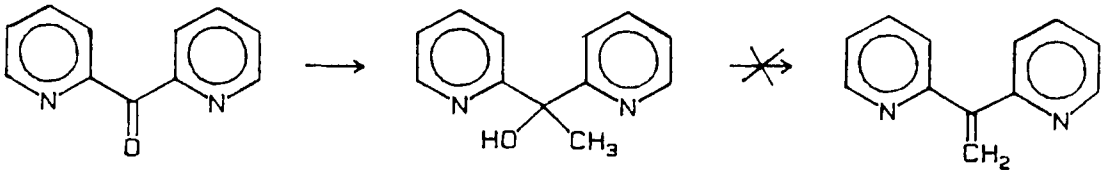
145 146

24. 1,1-Di(2-pyridyl)ethene (146). Method A.[126]

A stirred solution of methyltriphenylphosphonium bromide[127] (990mg, 2.8mmol) in anhydrous Et_2O was cooled to -70°C (Dry ice/ acetone bath) under a N_2 atmosphere, then *n*-BuLi (1.9mL, 3.1mmol; 1.6N/ *n*-hexane) was added at such a rate that the temperature did *not exceed -60*°C. The mixture was stirred vigorously for 30 minutes. Bis(2-pyridyl)ketone (**145**; 510mg, 2.8mmol) dissolved in anhydrous Et_2O (100mL) was added dropwise, then the solution was refluxed for two h, followed by quenching with water. The ether layer was separated, washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford (10%) **146**, as colorless oil[126]: 100mg; ^{1}H NMR δ6.05 (s, =C*H*$_2$, 2H), 7.30-7.65 (m, 3-5-py*H*, 6H), 8.61 (m, 6-py*H*, 2H).

Method B.[129] A suspension of oil-free NaH (120mg, 5.0mmol) and freshly distilled (from CaH_2) DMSO (50mL) was heated under a N_2 atmosphere to 70°C for about one h until the evolution of hydrogen ceased. The resultant yellow-green solution of sodium methyl-sulphinyl carbanion[128] was cooled in an ice-bath until it started to crystallize. Methyltriphenylphosphonium bromide (1.01g, 2.5mmol) in DMSO (50mL) was then added and the resultant solution was stirred at 20°C for 25 min by which time it had become dark red. On addition of *bis*(2-pyridyl)ketone (**145**; 510mg, 2.8mmol) into DMSO, the temperature rapidly rose to ca. 50°C. The solution was stirred at 60°C for one h, then the DMSO was removed by vacuum distillation. The residue, dissolved in 10% HCl, was extracted several times with $CHCl_3$ to remove the triphenylphosphine oxide.

The aqueous layer was made alkaline and extracted with $CHCl_3$. The red-brown $CHCl_3$ extract was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give a brown oil, which was purified by eluting with benzene on a column of neutral alumina. The resultant liquid was distilled to give (17%) 1,1-di(2-pyridyl)ethene (**146**), as an amber colored liquid[126]: 85mg.

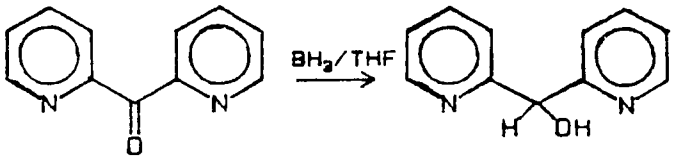


145 **147** **146**

Method C. *Bis*(2-pyridyl)ketone (**145**; 2.02g, 11mmol) dissolved in anhydrous Et_2O (150mL) under a N_2 atmosphere was added dropwise to a MeLi solution (7.5mL, 12mmol; 1.5N/*n*-hexane) cooled to -60°C. The temperature was maintained at -60±5°C by varying the depth of immersion in a dry ice/acetone slurry for one h. After the addition was complete, the mixture was allowed to warm to -20°C and maintained at -20±5°C for an additional h. This solution was quenched with MeOH/water and extracted with $CHCl_3$. The organic extract was washed with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl. The combined organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford (70%) 1,1-*bis*(2-pyridyl)ethanol (**147**)[129]: 1.54g; ^1H NMR δ1.99 (s, CH_3, 3H), 6.5 (bs, O*H*, 1H), 7.04-7.17 (m, 3-py*H*, 2H), 7.52-7.79 (m,

4,5-py*H*, 4H), 8.49 (dd, 6-py*H*, J=7.9, 1.4Hz, 2H); MS m/e 200 (M^+, 4), 185 (M^+-CH_3, 25), 183 (M^+-HO, 25), 122 (M^+-C_5H_4N, 100).

A stirred solution of alcohol **147** (980mg, 4.9mmol) in 80% H_3PO_4 (20mL) was heated to 130°C. With continued stirring, the temperature was raised to 150°C and maintained for 30 min. The resulting dark brown solution was cooled to 25°C and neutralized carefully with NaOH (24g). The aqueous layer was extracted with $CHCl_3$ and the extract layer was washed with aqueous saturated $NaHCO_3$ and dried over anhydrous $MgSO_4$. NMR and mass spectra data showed unidentified tarry materials including traces (<10%) of starting alcohol **147**.

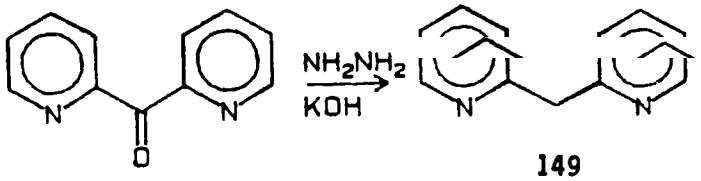


145 **148**

25. Di(2-pyridyl)methanol (148).

A stirred solution of **145** (57mg, 0.3mmol) in dry THF (30mL) was cooled to -70°C under a N_2 atmosphere. THF/Borane (400μL, 0.4mmol; 1.0N) was added with vigorous stirring. The solution was maintained at -70°C for one h, followed by thirty minutes at 25°C. The resulting dark brown solution was quenched with H_2O, then extracted with $CHCl_3$. The extract was washed aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and column chromatographed (silica gel, EtOAc) to give **148**, as colorless liquid: 23mg; R_f 0.15

(silica gel, EtOAc); ^{1}H NMR δ5.55 (bs, O*H*, 1H), 5.92 (s, C*H*OH, 1H), 7.05-7.22 (m, 3,5-py*H*, 4H), 7.46-7.63 (m, 4-py*H*, 2H), 8.31 (d, 6-py*H*, J=5.5Hz, 2H)], which was air oxidized[129] to give (40%) ketone **145**.

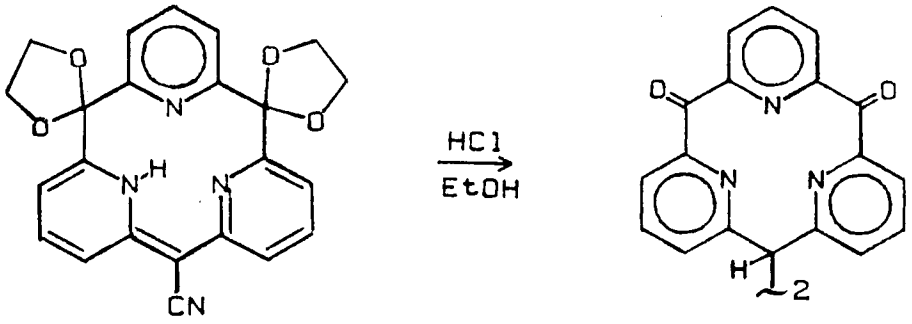


145 **149**

26. Di(2-pyridyl)methane (149).

Potassium hydroxide (1.1g) in diethylene glycol (20mL) was heated carefully under a N_2 atmosphere until KOH began to melt and dissolve, then the heat was removed until the exothermic process was completed.[130] After the solution was cooled to 80-100°C, **145** (790mg, 4.3mmol) and NH_2NH_2 (85%; 0.4mL, 10.6mmol) were added. The mixture was heated cautiously until any exothermic reaction was complete and then the distillate (ca. 5mL) was collected during reflux for 4 h. The cooled solution was poured into H_2O (50mL), neutralized with HCl (1N), and extracted with $CHCl_3$. The extract was washed with aqueous saturated NaCl and column chromatographed (silica gel, $CHCl_3$ to EtOAc) to give (71%) **149**, as colorless oil, which was unstable (*in vacuo*, a brown colored liquid resulted): 50mg; R_f 0.10 (silica gel, EtOAc); ^{1}H NMR δ4.35 (s, CH_2, 2H), 7.06-7.31 (m, 3,5-py*H*, 4H), 7.60 (td, 4-py*H*, J=7.5, 1.7Hz, 2H),

8.55 (dd, 6-py*H*, J=7.4, 1.0Hz, 2H); MS m/e 171 (M^++1, 2), 170 (M^+, 21), 169 (M^+-H, 100), 168 (M^+-2H, 12).



124 150

27. Dimer of 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5-dione (150).

A mixture of 124 (470mg, 1.1mmol) in concentrated HCl (10mL) and EtOH (10mL) was refluxed for 7 h. The resulting colorless solution was cooled to 0°C and neutralized with solid NaOH and extracted with $CHCl_3$. The extract was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. The resulting solid was column chromatographed (silica gel, $CHCl_3$; EtOH; 10% HOAc/EtOH) to afford crude 150, which was recrystallized (80%) from EtOH/$CHCl_3$: 380mg; mp 250°C (dec); ^{1}H NMR δ5.66 (s, C*HCH*, 2H), 7.02 (dd, 3-py*H*, J=7.5, 1.1Hz, 4H), 7.46 (t, 4-py*H*, J=7.5Hz, 4H), 7.71 (dd, 5-py*H*, J=7.5, 1.1Hz, 4H), 8.13-8.40 (m, 3′,4′-py*H*, 6H); ^{13}C NMR δ41.1 (*C*H), 121.5 (*C*3), 125.9 & 126.6 (*C*3′,5), 136.5 (*C*4), 137.9 (*C*4′), 147.1 (*C*2), 153.0 & 153.1 (*C*2′,6), 187.9 (*C*=O); MS m/e 601 (M^++1, 30), 600 (M^+, 77), 599 (M^+-H, 28), 572 (M^+-CO, 37), 544 (M^+-C_2O_2, 38), 516 (M^+-C_3O_3, 10), 466 (M^+-$C_7H_3O_2N$, 15), 389 (M^+-$C_{10}H_6N$, 26), 301 (1/2M^++H, 100), 300 (1/2M^+-CO, 27), 244 (1/2M^+-C_2O_2, 56), 217 (1/2M^+-C_3O_3, 28); Anal. Calcd. for

$C_{36}H_{20}N_6O_4 \cdot 1/2H_2O$; C, 70.93; H, 3.47; N, 13.93. Found: C, 70.47; H, 3.51; N, 13.68.

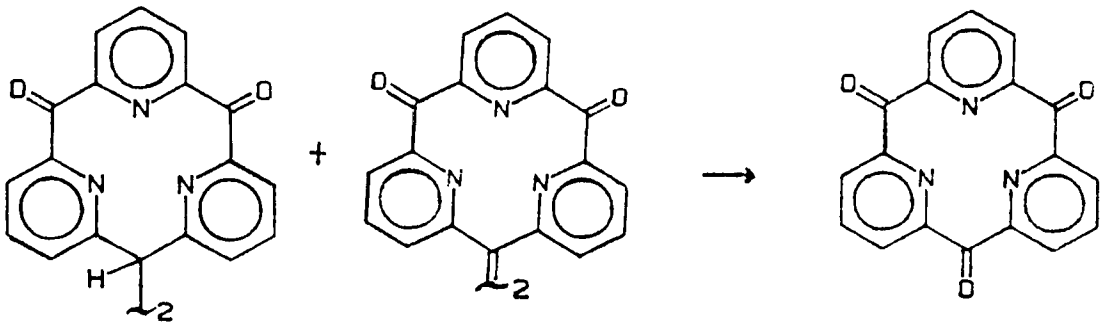
150 151

28. Dehydrogenation of 150. Method A.[132]

A solution of 150 (49mg, 0.08mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; 54mg, 0.24mmol) in dry toluene (30mL) was refluxed for 23 h under a N_2 atmosphere. The mixture was cooled and the white solid was filtered, then washed several times with toluene. The combined toluene fraction was washed with aqueous saturated Na_2CO_3 and then aqueous saturated NaCl. After drying over anhydrous $MgSO_4$ and evaporation of solvent, the residue was recrystallized from $CHCl_3$ to give (87%) 151: 43mg; mp 410°C (dec); ^1H NMR δ7.35 (dd, 3-py*H*, J=7,6, 1.2Hz, 4H), 7.62 (t, 4-py*H*, J=7.6Hz, 4H), 7.96 (dd, 5-py*H*, J=7.6, 1.1Hz, 4H), 8.15 (dd, 4′-py*H*, $J_{3',4'}=J_{4',5'}$= 7.8Hz, 2H), 8.42 (dd, 3′-py*H*, J=7.8, 1.1Hz, 4H); MS m/e 598 (M^+, 3), 597 (M^+-H, 4), 301 ($1/2M^+$+2H, 100); Anal. Calcd. for $C_{36}H_{18}N_6O_4 \cdot 1/2CHCl_3$: C, 66.60; H, 2.83; N, 12.77. Found: C, 67.04; H, 3.55; N, 12.92.

Method B. A stirred solution of 150 (105mg, 0.17mmol) in $CHCl_3$ (30mL) was aerated for 7 days. During aeration, $CHCl_3$ (10mL,

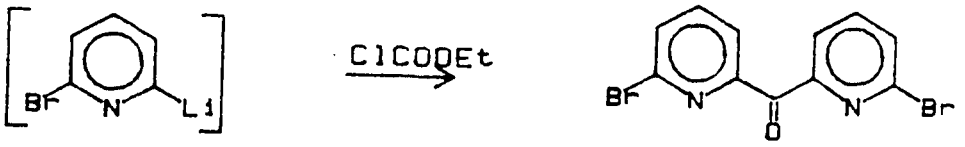
two times) was added and the white solid precipitated, which was identified as the crude **151**, which was recrystallized from $CHCl_3$ to afford (>99%) pure **151**: 103mg.



150 **151** **115**

29. 12<(2,6-Pyridino)$_3$-1$_3$-coronand-3>1,5,9-trione (115).

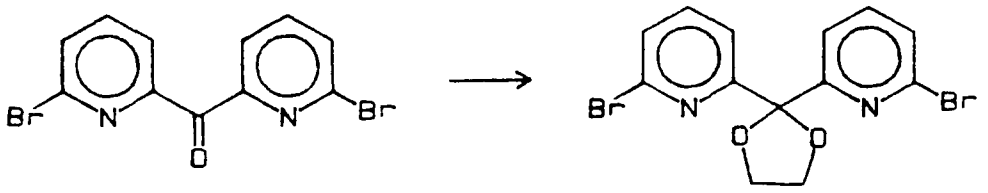
A mixture [^{1}H NMR indicated **150** (40%) and **151** (60%); 61mg, 0.1mmol] in glacial AcOH (30mL) and SeO_2 (200mg) was refluxed for 10 h. Additional SeO_2 (100mg) was added and the mixture was refluxed for another 24 h. After filtration of the Se• on a Celite pad and subsequent removal of the solvent *in vacuo*, the resultant colorless triketone **114** was column chromatographed (silica gel, $CHCl_3$ to 10% AcOH/EtOH). The eluent was washed with aqueous saturated $NaHCO_3$ and saturated NaCl, and evaporated *in vacuo* to afford crude triketone **115**, which was recrystallized from $CHCl_3$/EtOH to give (80%) **115**: 48mg.



141 140

30. *Bis*-2-(6-bromopyridyl)ketone (140).

A solution of 6-bromo-2-lithiopyridine (141; 80mmol) was cooled to -65°C (dry-ice/acetone), then ethyl chloroformate (4.37g, 40mmol) dissolved in anhydrous Et_2O (100mL) was added dropwise at such a rate that the temperature did not exceed -60°C. The mixture was stirred vigorously for two h, then quenched with MeOH, followed by addition of 2.0N HCl. The mixture was refluxed for two h, neutralized with aqueous saturated Na_2CO_3, and extracted with $CHCl_3$. The extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford 140, as a beige residue, which was chromatographed (silica gel, DCM): 8.69g (63%); mp 152-153°C (lit.[121a] mp 155-156.5°C); ^1H NMR δ7.70 (d, 5-py*H*, J=2.6Hz, 2H), 7.72 (d, 3-py*H*, J=6.0Hz, 2H), 8.08 (dd, 4-py*H*, J=6.0, 2.6Hz, 2H).



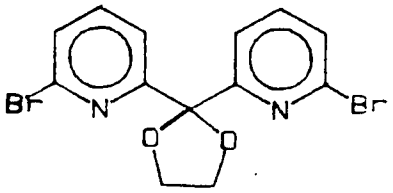
140 126

31. 2,2-*Bis*-2'-(6'-bromopyridyl)-1,3-dioxolane (126).

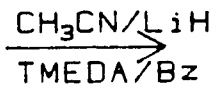
Method A.[121c] A slurry of *bis*-2-(6'-bromopyridyl)ketone (140) (980mg, 2.9mmol), anhydrous Li_2CO_3 (5.0g), and 2-bromoethanol (30mL), as reactant and solvent, was refluxed gently for five hr under a N_2 atmosphere. Excess 2-bromoethanol was removed by vacuum distillation and the cooled residue was poured into an aqueous Na_2CO_3 (5%, 400mL), which was then extracted with $CHCl_3$. The organic extract was dried over anhydrous $MgSO_4$, passed through a column (silica gel, DCM), and concentrated *in vacuo* to give a viscous beige oil, which was triturated with ice-cold EtOH, then recrystallized from EtOH/$CHCl_3$ to afford (38%) ketal 126, as colorless rhombohedra: 420mg; mp 145-146°C (lit.[121c] mp 146-148°C); ^1H NMR δ4.15 (s, CH_2, 4H), 7.38 (dd, 3/5-py*H*, J=6.9, 1.6Hz, 2H), 7.57 (t, 4-py*H*, J=7.2Hz, 2H), 7.80 (dd, 5/3-py*H*, J=6.4, 1.6Hz, 2H).

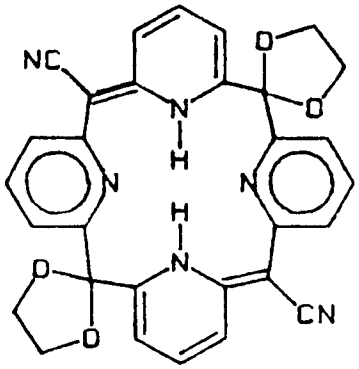
Method B.[119a] A mixture of 140 (880mg, 2.6 mmol) was treated according to Method A, except for the use of 2-chloroethanol (30mL) and a reflux period of three days, to give (12%) ketal 126: 120mg.

Method C.[131] A mixture of 140 (9.90g, 29.2mmol), freshly distilled ethylene glycol (10mL), and concentrated H_2SO_4 (10 drops, 0.5mL) in anhydrous toluene (200mL) was refluxed gently for 10 days. Water was removed by means of a Dean-Stark water separator. The mixture was cooled to 25°C and poured into ice-cold aqueous saturated $NaHCO_3$. This suspension was filtered and the aqueous solution extracted several times with $CHCl_3$. The combined organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give the resulting yellow solid, which was recrystallized from $EtOH/CHCl_3$ to afford (90%) 126: 10.10g.



126



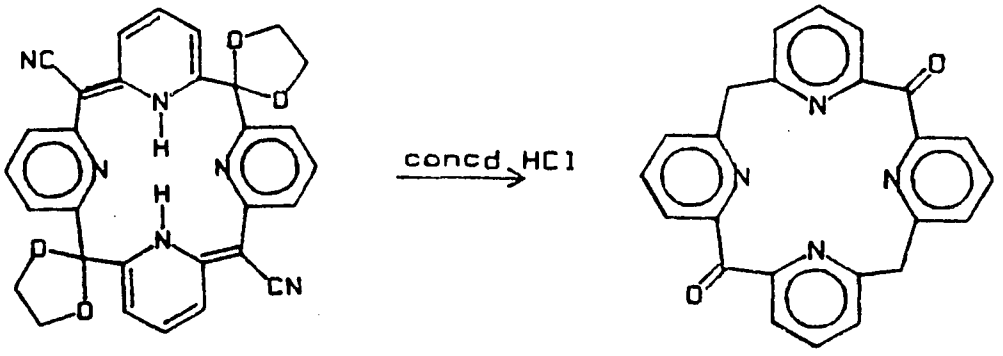


127

32. 16<(2,6-Pyridino)$_4$-1$_4$-coronand-4>1,9-dicyano-5,13-dione Ethylene Glycol Bisketal (127).

A mixture of LiH (520mg), dry MeCN (10mL), dibromoketal 126 (2.03g, 5.3mmol) in redistilled TMEDA (13mL), and anhydrous benzene (250mL) was refluxed for 2 days under a N_2 atmosphere. The dark brown mixture was quenched with water. The organic solvent was removed *in vacuo* and aqueous HCl (0.1N) was added until the aqueous layer remained acidic. The aqueous layer was extracted with $CHCl_3$.

The combined organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo* to give a yellow solid, which was chromatographed (ThLC, alumina, DCM) and recrystallized from DCM/cyclohexane to afford (22%) cyclotetrapyridine **127**: 300mg; mp 390°C (dec); R_f 0.39 (alumina, DCM); ^1H NMR δ4.24 (m, CH_2, 8H), 6.90 (m, 3-py*H*, 4H), 7.36 (m, 4,5-py*H*, 8H), 15.04 (bs, N*H*, 2H); ^{13}C NMR δ65.0, 65.5 (*C*H_2), 70.4 (*C*C≡N), 105.4 (O*C*O), 110.0 (*C*3), 120.1 (*C*5), 122.1 (*C*≡N), 136.9 (*C*4), 151.3 (*C*6), 154.9 (*C*2); IR (KBr) 2190cm^{-1} (C≡N); MS m/e 531 (M^++1, 29), 530 (M^+, 100), 486 (M^+-C_2H_4O, 8), 458 (M^+-$C_3H_4O_2$, 42), 442 (M^+-$C_4H_8O_2$, 17), 414 (M^+-$C_5H_8O_3$, 31); Anal. Calcd. for $C_{30}H_{22}N_6O_4 \cdot 1/2CH_2Cl_2$: C, 63.93; H, 4.05; N, 14.67. Found: C, 63.47; H, 3.65; N, 14.37.

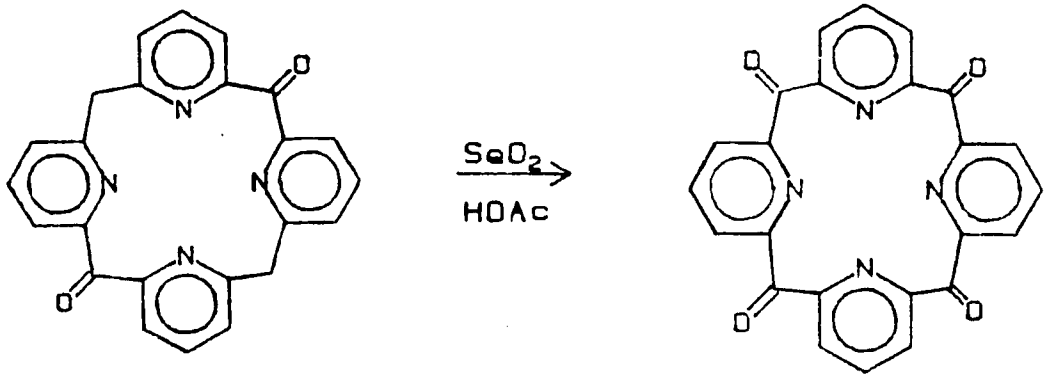


127 **152**

33. 16<(2,6-Pyridino)$_4$-1$_4$-coronand-4>1,9-dione (152).

A solution of cyclotetrapyridine **127** (200mg, 0.4mmol) and concentrated HCl (20mL) was refluxed for 10 h, then neutralized with solid NaOH and extracted with $CHCl_3$ (2x500mL). The organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, concentrated *in vacuo* to afford impure diketone

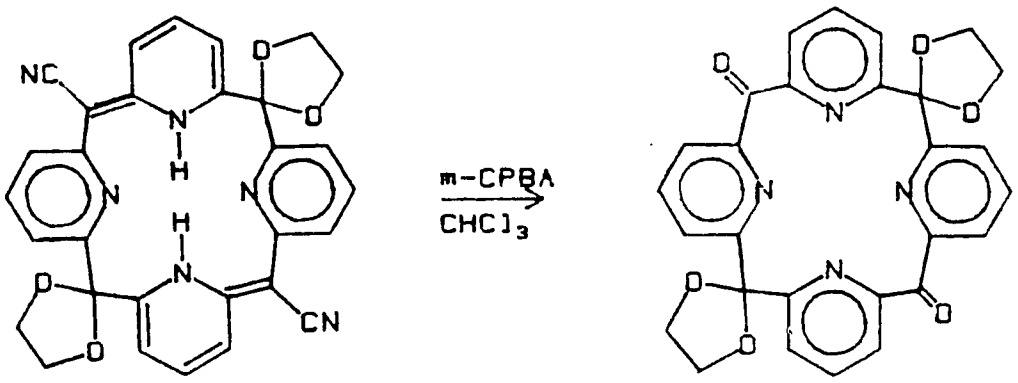
152, as colorless solid, which was unstable (easily oxidized): ^{1}H NMR δ4.09 (d, C*H*$_2$, J=3.8Hz, 4H), 6.9-7.8 (m, py*H*, 12H); MS m/e 393 (M^++1, 33), 392 (M^+, 93), 363 (M^+-CHO, 100), 336 (M^+-C_2O_2, 28), 335 (M^+-C_2HO_2, 26). This dione was not purified further but immediately oxidized to 125.



152 125

34. 16<(2,6-Pyridino)$_4$-1$_4$-coronand-4>1,5,9,13-tetraone (125).

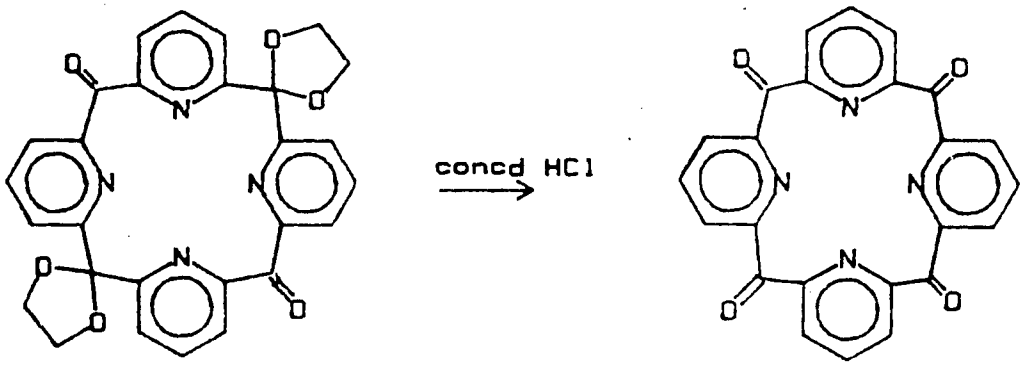
A suspension of impure diketone 152 (180mg, 0.4mmol), SeO_2 (100mg), and glacial AcOH (20mL) was refluxed for 10 h. The mixture was diluted with EtOH (40mL) and column chromatographed on silica gel eluting with HOAc/EtOH (50:50) then $CHCl_3$. The eluent was neutralized with aqueous saturated Na_2CO_3, washed with aqueous saturated NaCl, and evaporated *in vacuo* to give crude tetraketone 125, which was recrystallized from $CHCl_3$/EtOH to give (80% from 127) 125, as colorless needles: 150mg; mp 380°C (dec); ^{1}H NMR (400MHz) δ7.89-7.94 (m, py*H*, 12H); ^{13}C NMR δ125.7 (*C*3), 137.8 (*C*4), 155.1 (*C*2), 195.0 (*C*=O); MS m/e 421 (M^++1, 29), 420 (M^+, 100), 336 (M^+-C_3O_3, 80), 308 (M^+-C_4O_4, 57); Anal. Calcd. for $C_{24}H_{12}N_4O_4$: C, 68.57; H, 2.88; N, 13.33. Found: C, 67.00; H, 3.34; N, 12.94.



127 153

35. 16<(2,6-Pyridino)$_4$-1$_4$-coronand-4>1,5,9,13-tetraone Ethylene Glycol Bisketal (153).

To a stirred ice-cooled solution of cyclic tetrapyridine **127** (54mg, 1.0mmol) in $CHCl_3$ (30mL), was added *m*-chloroperbenzoic acid (460mg, 85% purity, 2.1mmol) over 30 min. After 4 h at 25°C, the resulting colorless solution was sequentially washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl. The $CHCl_3$ extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford crude diketal **153**: ^{1}H NMR δ4.06 (s, CH_2, 8), 7.40-7.71 (m, py*H*, 9H); MS m/e 508 (M^+, 7), 465 (M^+-C_2H_3O, 36), 419 (M^+-$C_4H_9O_2$, 46), 393 (M^+-$C_5H_9O_3$, 10), 364 (M^+-$C_6H_8O_4$, 14), 336 (M^+-$C_7H_8O_5$, 24). Further purification of **153** was not successful because of low solubility.



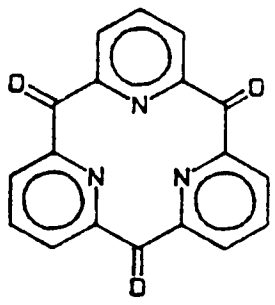
153 125

36. 16<(2,6-Pyridino)$_4$-1$_4$-coronand-4>1,5,9,13-tetraone (125).

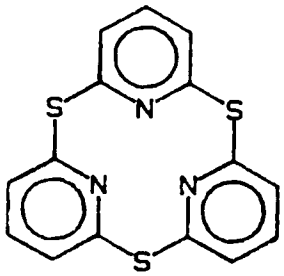
A mixture of crude diketal **153** (500mg, 1.0mmol) in concentrated HCl (50mL) was refluxed vigorously for 36 h, then additional concentrated HCl (10mL) was added (4X) every 8 h. The acidic solution was neutralized with solid NaOH and extracted with $CHCl_3$ (2x500mL). The $CHCl_3$ layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a colorless solid, which was recrystallized from $CHCl_3$/EtOH to give (70% from **127** tetraketone **125**, which was identical to the previously prepared sample: 300mg.

VII. Results and Discussion

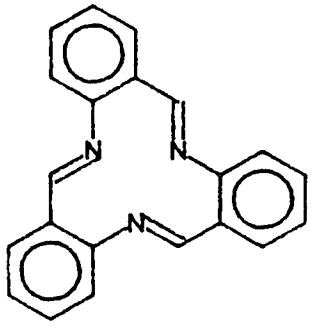
Our main research goal was the synthesis and characterization of the first pyridinophane **115** and its homologs. Trione **115** was surmised to possess a notable core-strain attributed to *N-N*-interactions within the cavity, but by coupling the rings with polarized carbon atoms, an electron rich core would be produced. Although related macrocycles **116**[116] and **117**[117] have been synthesized, these 12-membered rings all possess non-planar conformations and, as such, are limited in their specific metal ion chelation and were poor models to assess the lone pair interaction(s). The introduction of planar sp^2-bridge functionalities such as carbonyls, should force the macrocycle into a rigid, planar, or nearly so, structure. Any deviation from planarity would be predominantly caused by the *N*-lone pair interactions. Inspection of a CPK models of **115** indicated that a planar conformation with a minimum of steric interactions was nevertheless plausible.



115

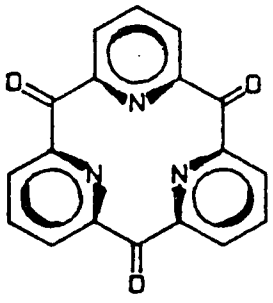


116

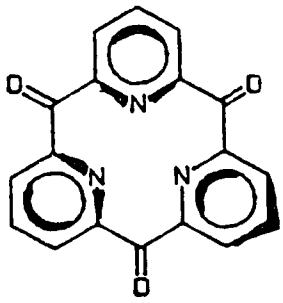


117

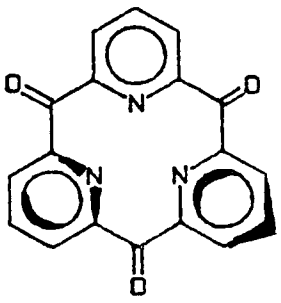
The inherent structural rigidity and high electron density within the cavity should enhance the chelating characteristics of **115** in at least two ways. Firstly, the pyridine *N*-lone electron pairs will be directed into the cavity of these potentially planar macrocycles, thus a high Lewis basicity is expected. Based upon structural information from the related sulfur-bridged macrocycle **116**,[116] the *N*-lone electron pair density of the three rings is predicted to be greater than the effective cavity volume of trione **115**; thus, the extent of direct *N*-electron interactions can be related to the degree of deviation from planarity. If the rings are planar, the size, shape and volume of *N*-lone pair electron orbitals must be reduced. Several conformations are possible; the first option, **115a**, aligns *N*-lone pairs up and on the same side of the molecule. The second option, **115b**, suggests that two *N*-lone pairs are tipped out-of-the-plane on one side of the molecule, and the third is tipped in the opposite direction. The third option, **115c**, defines a non-planar, helical conformation with C_s symmetry, in which the *N*-lone electron pairs are directed sequentially above, in the plane, and below the plane-of-the-molecule. These



115a



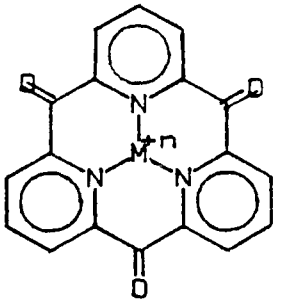
115b



115c

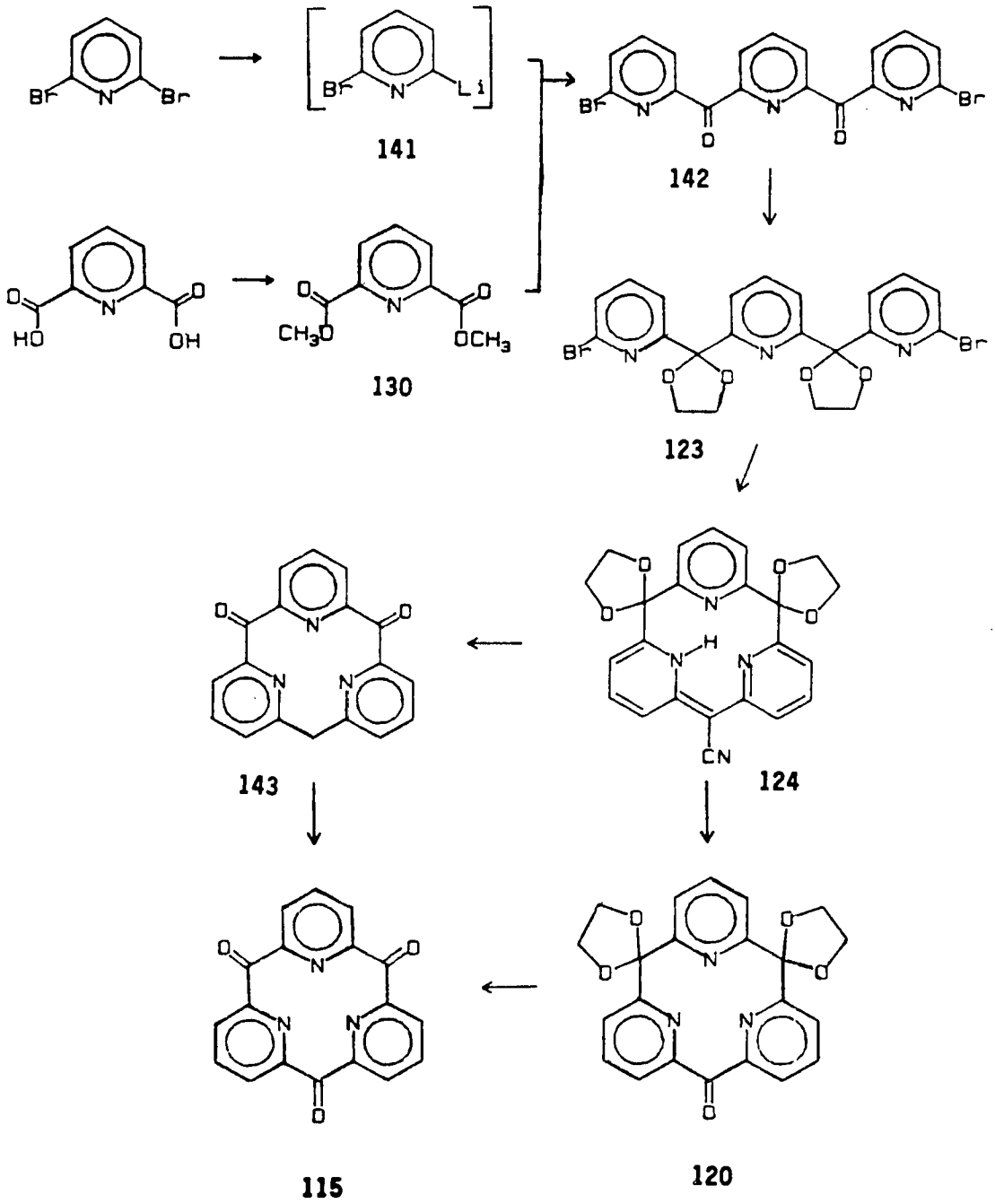
conformations are fixed by the high barrier to rotating an electron pair through the cavity of the molecule.

Secondly, enhanced selectivity in metal ion inclusion is expected because the non-bonding electrons are held in a fixed orientation within a limited radius. Thus only cations, which will fit into or onto the ring cavity, would be stabilized by chelation. The radius of the ring can be adjusted by increasing the number of atoms in the macrocycle, thus it should be possible to "tailor" the cavity to custom fit a small "guest". The ability to "tailor" a host cavity to "custom fit" a guest is greatly diminished in the corresponding non-rigid ligands, which can easily redirect the *N*-electron pairs *via* minor conformational changes. If the electron pairs are redirected toward cation; the ligand interaction would be stronger, but less selective.



The general route to the initial target **115** is illustrated in Scheme 6. The discussion is subdivided into the major transformations necessary for a logical progression for the total synthesis. The over-all construction of these novel macrocycles is discussed from the standpoint of previously documented model reactions. The subdivisions utilized in this discussion are (in order): (1)

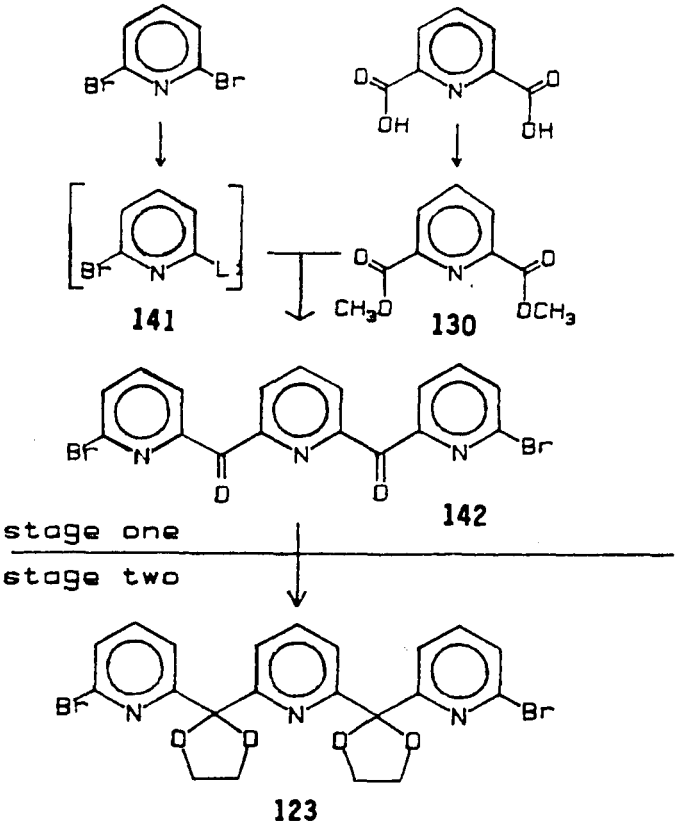
Scheme 6.



syntheses of pyridyl ketone ketals; (2) α-carbanion formation of acetonitriles; (3) cyclization to form [1_3](2,6)pyridinophanes; (4) modification of trione **115**; (5) self-dimerization of **143** and dehydrogenation of its dimer (**150**); (6) synthesis of tetraketone **125**; and (7) transition metal complexation of trione **115**.

VII-1. Syntheses of Pyridyl Ketone Ketals

Fabrication of a key precursor (**123**) was accomplished by a classic two-stage sequence from readily available starting materials, 2,6-dibromopyridine and 2,6-di(methoxycarbonyl)-pyridine (**130**). Stage one involved the reaction of the substituted



lithiopyridine 141 with diester 130, then in stage two the carbonyl groups were ketalized to afford *bis*-ketal 123.

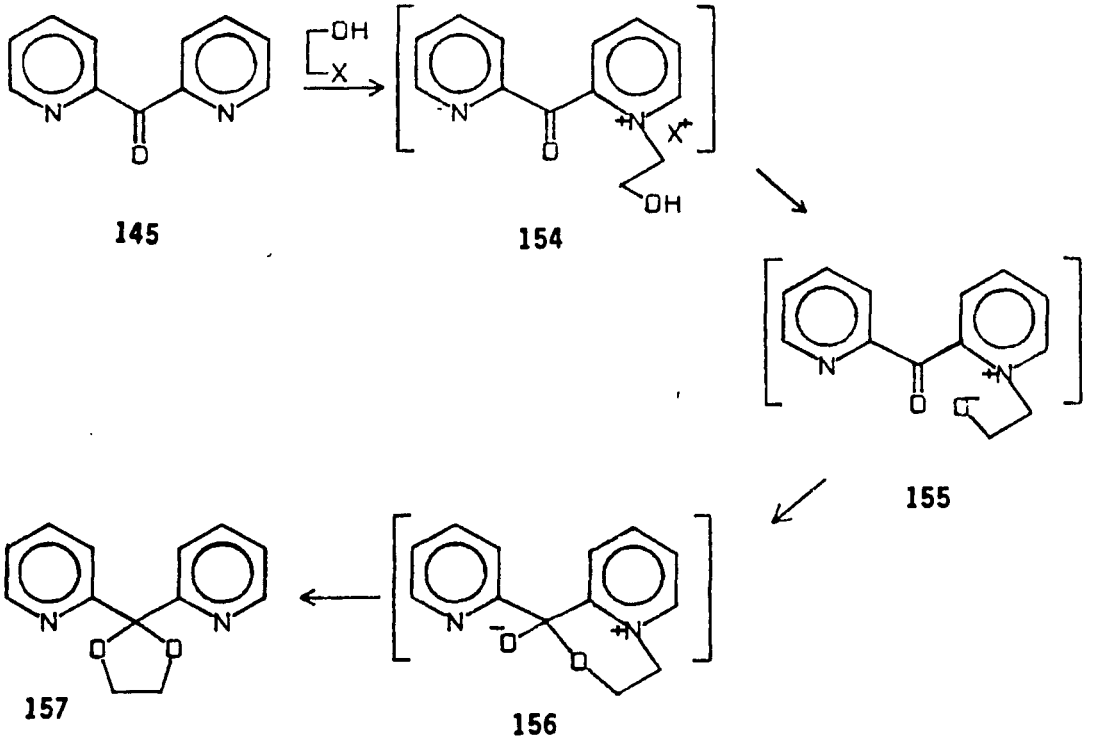
Early work by Holm et al.[121b,c] indicated that treatment of 2,6-dibromopyridine with alkyllithiums *via* an entrainment procedures[121a] generated (≥82%) 6-bromo-2-lithiopyridine (141). Elaboration of this technique by Newkome et al.[119,121d-g] showed that 2,6-dibromopyridine, when treated with *n*-butyllithium in ether at low temperatures, quantitatively generated pyridyllithium 141. However, 141 is *only stable at low temperature* (<-80°C); at elevated temperature (>-60°C), spontaneous decomposition gave a myriad of unknown products. In THF, a facile *bis*-metal-halogen exchange occurred at <-80°C; again at elevated temperature (>-60°C), decomposition occurred. Thus, all reactions involving intermediate 141 were conducted at -78°C (dry-ice acetone bath).

Treatment of dimethyl 2,6-pyridinedicarboxylate (130) with 141 in either diethyl ether or THF at -80°C gave (40%) of 2,6-*bis*[2′-(6′-bromopicolinoyl)]pyridine (142). The NMR and mass spectra of diketone 142 were consistent with the proposed structure. The ^{1}H NMR spectrum of 142 was nearly first order showing a doublet at δ7.48 for 5′-py*H*, a triplet at δ7.82 for 4′-py*H*, and a multiplet at δ8.04-8.21 including a doublet at δ8.36 for 3-py*H*. The MS data for 142 were dominated by three peaks at m/e 449, 447, and 445, corresponding to the isotopically different molecular ions possessing the appropriate 8:17:8 ratio of the relative intensities.

Ketalization of 142 was essential to prevent concomitant nucleophilic addition to the carbonyls during the cyclization step.

Ketalization of pyridyl ketones has been studied in detail by Sauer[119a] and shown to proceed under basic conditions. This is a novel twist to the traditional acid-catalyzed ketalization procedures. Base-catalyzed ketalization of model pyridyl ketone **145** with 2-chloro(or bromo)ethanol was proposed[121c] to proceed *via* the mechanism shown in Scheme 7. Initial *N*-quaternization with 2-haloethanol afforded complex **154**. The intermediate interacted with lithium carbonate to generate zwitterion **155**, which could attack the carbonyl intramolecularly to yield intermediate **156**. Subsequent cyclization of **156** *via* nucleophilic displacement of a pyridine moiety generated (45%) 1,3-dioxolane **157**.

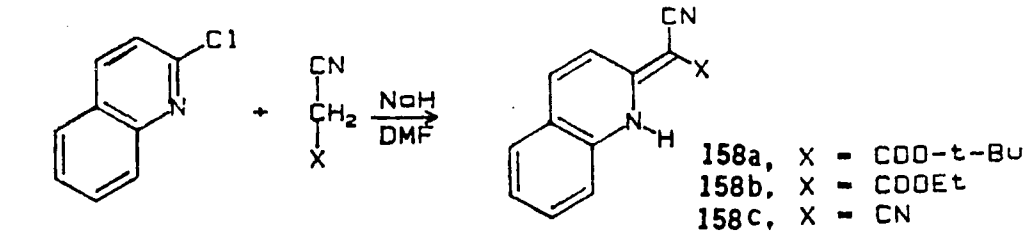
Scheme 7



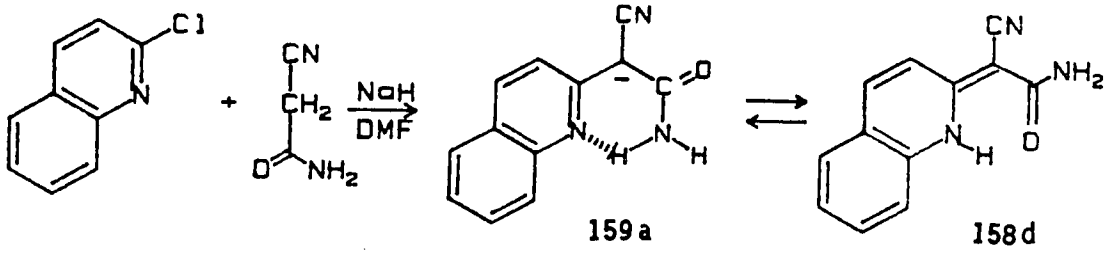
Base-catalyzed ketalization of **142** using 2-chloro- or 2-bromoethanol afforded less than 40% of **123** and required a labor intensive isolation procedure to remove the last traces of the haloalcohol and other side products. Thus, the more traditional acid catalyzed ketalization[131] of **142** *via* ethylene glycol was found to be preferable, in that treatment of **142** with *freshly distilled* ethylene glycol and a catalytic amount of concentrated H_2SO_4 in refluxing dry toluene for *ten days* afforded (70%) **123**. Ketal **123** was easily recrystallized from a mixture of EtOH and $CHCl_3$ and was identified (^{1}H NMR) by the spike at δ4.10 for ketal hydrogens. The loss of the carbonyl absorption (IR; 1685, 1320cm^{-1}) in **123** during this protection process further confirmed the transformation.

VII-2. α-Carbanion Formation of Acetonitriles

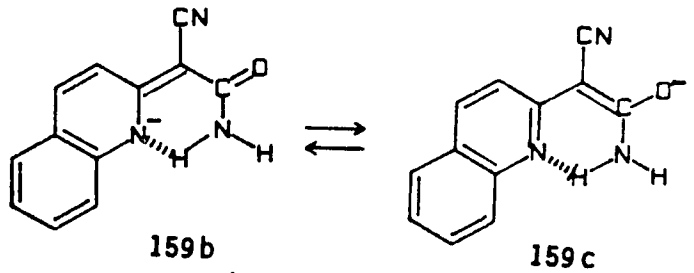
2-Chloroquinoline reacted[133] smoothly with either *tert*-butyl or ethyl sodiocyanoacetate or sodiomalononitrile to give either *tert*-butyl (**158a**), ethyl cyano-2(1*H*)-quinolylideneacetate (**158b**), or 2(1*H*)-quinolylidenemalononitrile (**158c**), respectively. However, the reaction of 2-chloroquinoline with the sodiocyanoacetamide did *not* give the expected product, cyano-2(1*H*)-quinolylideneacetamide (**158d**), under these conditions. Instead an orange, high-melting 2-quinolyl-(2*H*)-quinolylideneacetonitrile (**160**) was obtained in 34% yield. The conjugated structure was confirmed by a shift in the nitrile absorption to 2200 cm^{-1} (IR) and the intense UV-visible



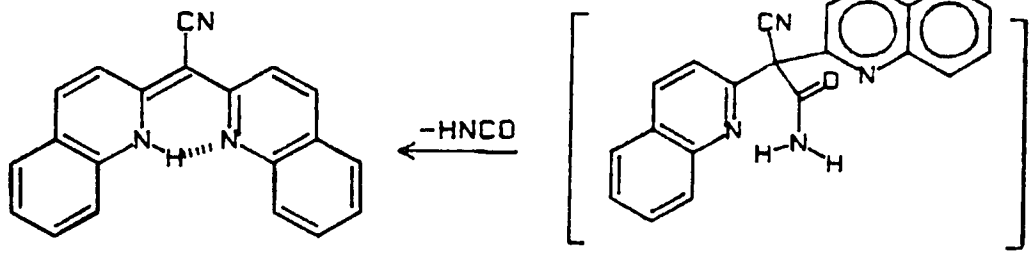
158a, X = COO-t-Bu
158b, X = COOEt
158c, X = CN



159a 158d



159b 159c

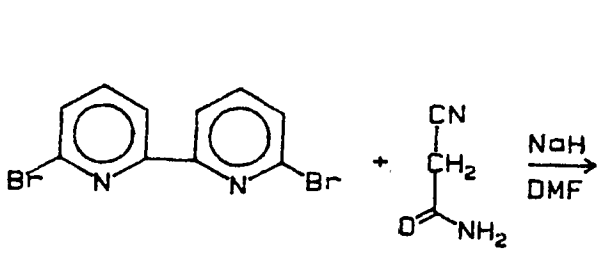


160 159d

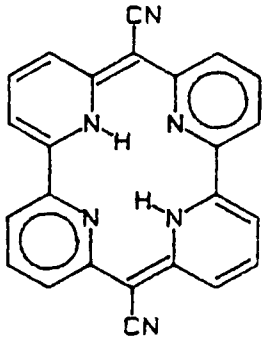
absorption spectra; λ_{max}276 ($CHCl_3$, logϵ=4.37), 322 (4.17), 363 (3.84), 382 (3.90), 432 (4.23), 456 (4.43), and 485 (4.33).

A plausible mechanism[133] for this anomalous transformation involved the formation of **158d**, which with strong base was converted to anion **159b**. Subsequent reaction of **159b** with 2-chloroquinoline gave 2,2′-diquinolylcyanoacetamide (**159d**). A novel elimination of isocyanic acid, initiated by intramolecular abstraction of a proton from the amido NH_2 of **159d**, would generate the extremely stable *meso*-cyanide **160**. This proposed mechanism was supported by the isolation of sodium cyanate and by trapping intermediate **158d** when the reaction was conducted at 50°C for one hour.

Similarly, the reaction between sodiocyanoacetamide and 6,6′-dibromo-2,2′-bipyridine (**94**) gave (20%) cyclo-*bis*-2-pyridyl-2′(1*H*)-pyridylideneacetonitrile (**95**), which showed absorption maxima (in 1-chloronaphthalene) at 357nm (ϵ36,600), 375 (37,000), 508 (7,000), 541 (5,600), and 592 (3,000) indicative of a highly conjugated system, and conjugated nitrile absorption (IR) at 2180 cm^{-1}.[100]



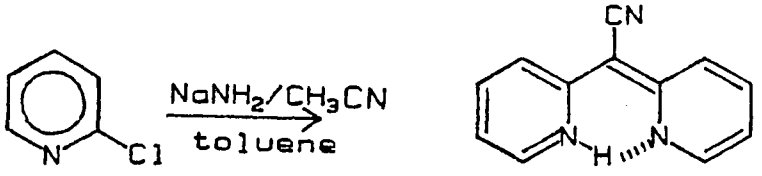
94



95

Condensation of halopyridines with acetonitrile produced a class of compounds called *quinolylmethanes*[103], which consist of methane and its derivatives in which two or three hydrogen atoms are substituted by six-membered heterocycles (i.e. pyridine, quinoline or benzoquinoline). Quinolylmethanes are the fundamental building blocks of many cyanine dye stuffs, presumably due to the formation of tautomeric species. Mesomerically stabilized colored forms are produced from the colorless species by the rehybridization of a bridging sp^3- to sp^2-carbon with a concurrent intramolecular proton shift. As part of a program directed to the syntheses of (2,6)pyridinophanes, the syntheses of *meso*-cyano compounds (or quinolylmethanes) were studied for insight into their physical and chemical properties, such as their tautomeric behavior and reactivity towards hydrolysis and/or oxidation.

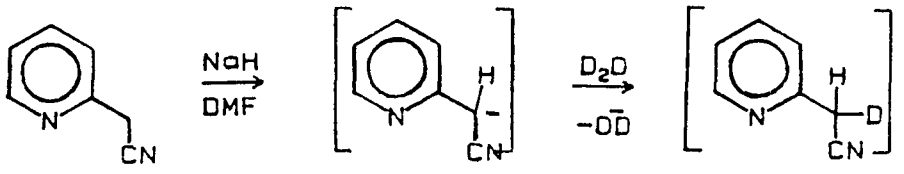
Significant early contributions to the synthesis and characterization of quinolylmethanes were made systematically by Scheibe.[113] For examples, *bis*(2-pyridyl)acetonitrile (128), the simplest *meso*-cyanide (or quinolylmethane), was prepared (12%) by heating 2-chloropyridine with $NaNH_2$ and CH_3CN in dry toluene.[113] The symmetrical di-[2-(or 4-)quinolyl]acetonitriles were also



128

prepared by heating 2- or 4-haloquinoline with $NaNH_2$ and CH_3CN, respectively.

Since pyridine is a π-deficient heteroaromatic molecule (Chap. III), the pyridyl group can be substituted for typical electron-withdrawing groups in order to activate the hydrogen of acetonitrile. Thus when 2-pyridylacetonitrile was treated with NaH in DMF, then quenched with D_2O, both methylenic hydrogens exchanged. Apparently, the exchange was promoted by formation of an α-carbanion intermediate **161**, which should undergo an acid-base interaction with D_2O to yield **162**.

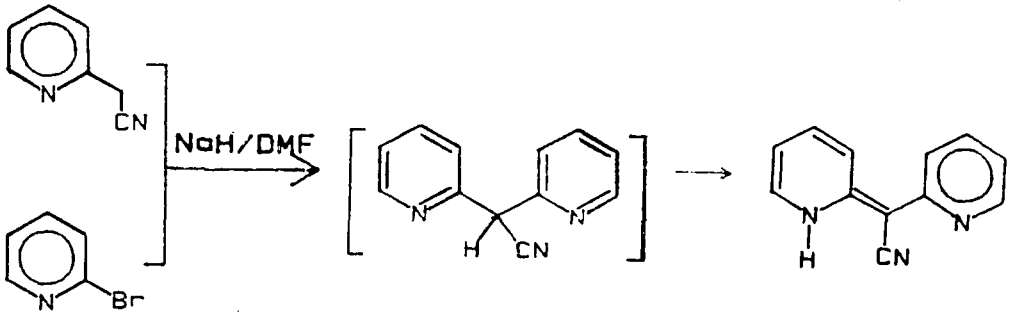


161

162

Heating 2-pyridylacetonitrile with NaH and 2-bromopyridine in dry DMF gave (73%) the *bis*(2-pyridyl)acetonitrile (**128b**), as yellow fibers. The mesomerically stabilized colored form **128b** was produced from the colorless tautomer **128a** by rehybridization of

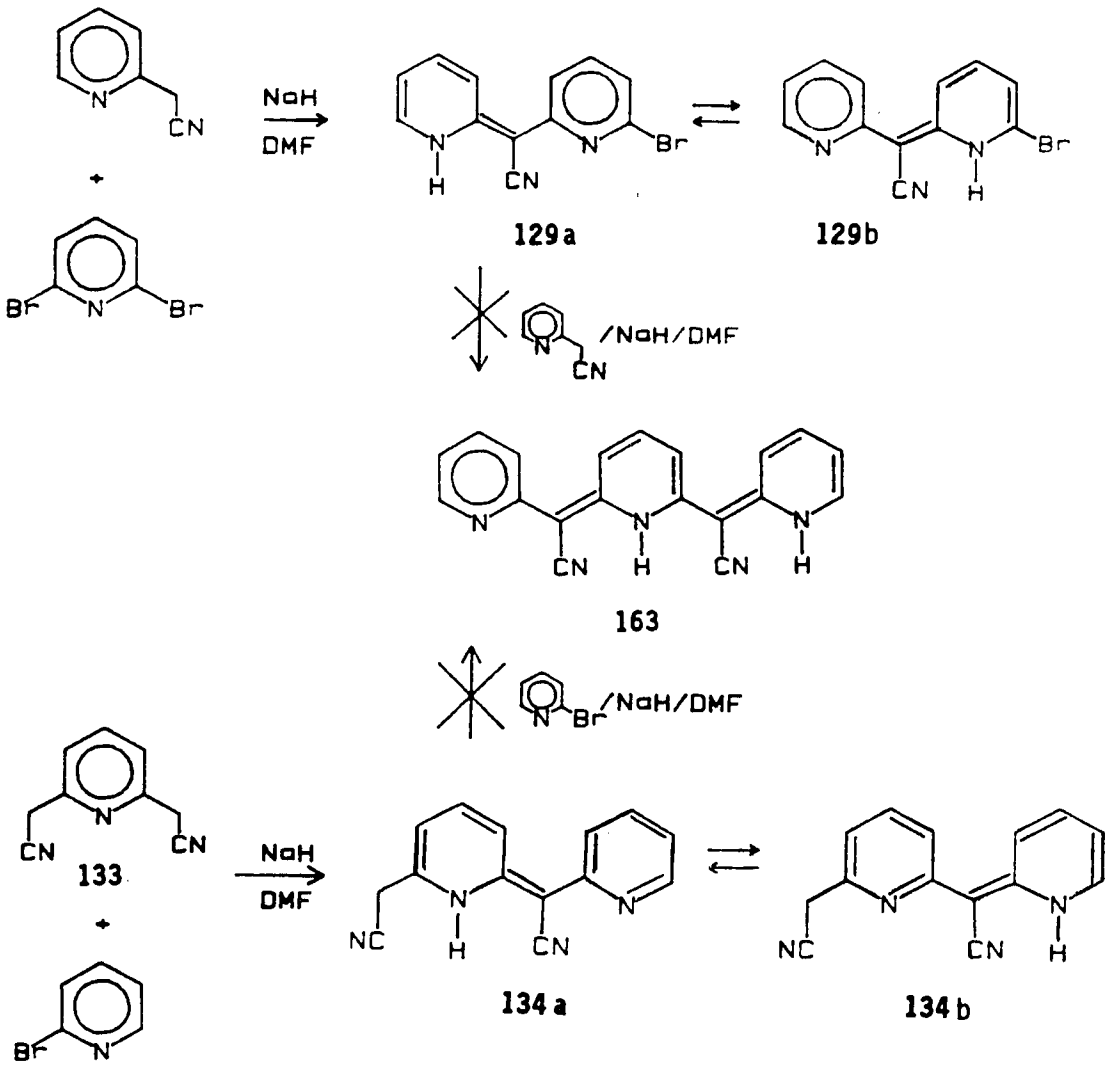
bridging the sp^3- to sp^2-carbon *via* an intramolecular proton shift. The ^{1}H NMR spectrum of **128b** showed a broad singlet at δ16.3 (lit.[113] δ16.1) indicative of a strong N-H••N interaction; this proton was not readily exchanged with D_2O at 25°C. Only two signals could be identified in the aromatic region; two doublets of triplets at δ6.60 and 7.91 for the 5-py*H* and 6-py*H*, respectively. Support for tautomerization in **128b** was shown in the ^{13}C NMR data; seven signals for the pyridine and nitrile carbons appeared at expected position, however, the methine bridge carbon appeared at δ67.5. The reduced frequency of the nitrile in the IR spectrum was also indicative of extended aromatic conjugation.



128a **128b**

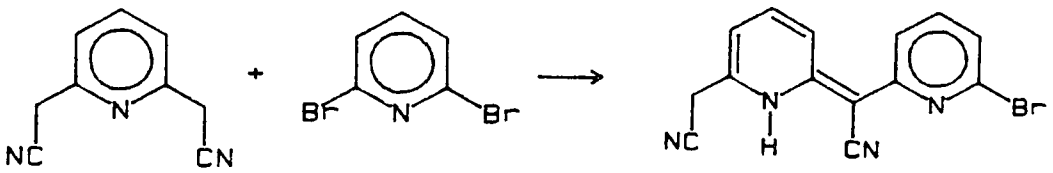
An analogous reaction was conducted with 2-pyridylacetonitrile and 2,6-dibromopyridine in order to synthesize the desired **163**. However, under these conditions, no tripyridine **163** was formed; instead, **129** was isolated (81%), as yellow fibers. The ^{1}H NMR spectrum of **129** exhibited the characteristic broad singlet at δ15.1 indicative of the N-H••N interaction and ^{13}C NMR data showed twelve signals including the unique signal at δ68.4 for the methine bridge

carbon. A nitrile absorption (IR) at 2185 cm^{-1} was again characteristic of a conjugated nitrile. The MS data were dominated by two peaks at m/e 275 and 273 with the ratio (4:5) of the relative intensities, corresponding to the isotopically different molecular ions.



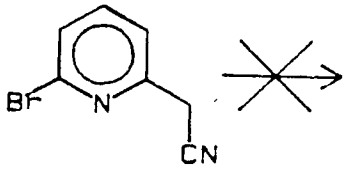
The reaction conditions were modified (reaction times, solvents/temperatures, base-catalysts); all to no avail! At this junction, a different tack was attempted in which the sodium salt of *bis*(2,6-cyanomethyl)pyridine (133) and 2-bromopyridine were considered. This procedure was, however, unsuccessful in that *only* 2-pyridyl-2'-(6'-cyanomethylpyridyl)acetonitrile (134) could be isolated in 36% yield. This structural assignment was confirmed by its ^{1}H NMR spectrum which showed a singlet at δ4.00 for cyanomethylene and a characteristic broad singlet at δ15.8 for the N-H proton. Further supportive ^{13}C NMR data for 134 showed fourteen signals including the methine carbon at δ75.5. The IR spectrum displayed both conjugated and unconjugated nitrile absorptions at 2180 and 2250cm^{-1}, respectively.

The initial synthetic route to heteromacrocycle 164 was designed so that the α-carbanion would self-condense with the α-pyridyl bromide. The reaction was conducted at a carefully controlled temperature (120°C) in DMF to prevent solvent decomposition. After work-up, the desired macrocycle 164 was not detected but instead the dipyridine 135 was isolated in 75% yield, as yellow fibers. The ^{1}H NMR spectrum of 135 exhibited a broad singlet (δ15.6), which integrated for one proton, typical for the hydrogen bonded N-H. The MS data were dominated by two peaks at m/e 314 and 312, corresponding again to the isotopically different molecular ions.

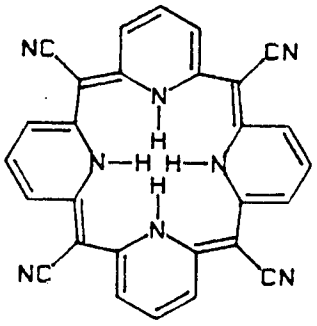


133

135



138

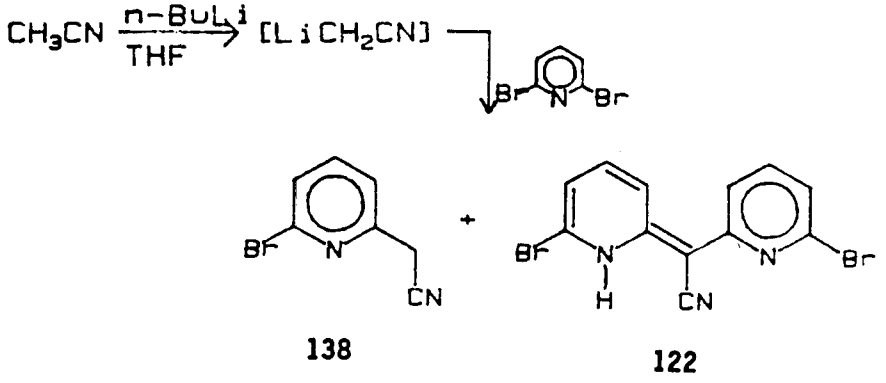


164

This problem had been envisioned; thus the precursor (138) for an alternate route had been synthesized. Abstraction of an α-hydrogen from acetonitrile was realized in liquid ammonia by means of sodium amide to generate the desired sodioacetonitrile as demonstrated by subsequent alkylation[134] and benzoylation.[135] Successful monoalkylations of primary nitriles employed strong bases, such as: alkali metal amides, dialkylamides, *bis*(trimethylsilyl)amides or alkyl (or aryl)lithium[103] to give high concentrations of the requisite nitrile carbanions, which were trapped by reaction with reactive primary or secondary alkyl halides.

In the hopes of utilizing an acetonitrile arylation in the ultimate synthesis of *bis*-2-(6-bromopyridyl)acetonitrile (122), *n*-BuLi in *n*-hexane was used to generate lithioacetonitrile at

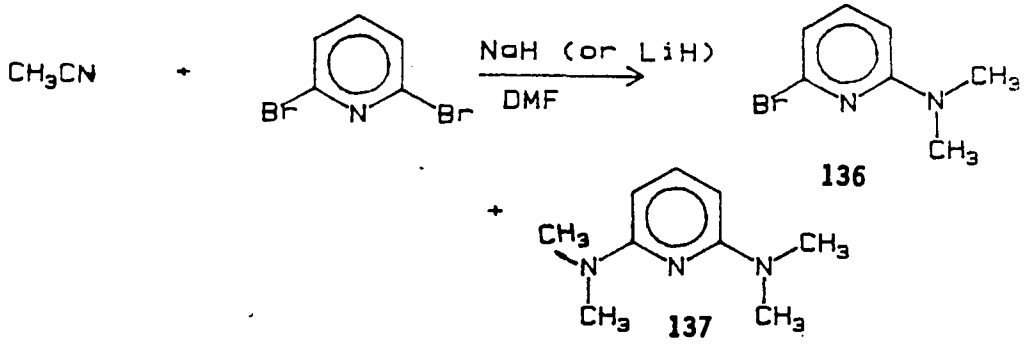
-70°C. A mixture of lithioacetonitrile with 2,6-dibromopyridine gave (27%) 2-(6-bromopyridyl)acetonitrile (138); only traces of the desired 122 were observed. The ^{1}H NMR spectrum of 138 exhibited a singlet which integrated for two protons at δ3.93 for cyanomethylene. The ^{13}C NMR spectrum showed seven signals, and the MS data were dominated by the two expected peaks at m/e 198 and 196 for the molecular ions. When 138 was treated with NaH in DMF, the desired 164 was not isolated, 138 was recovered unchanged.



138 122

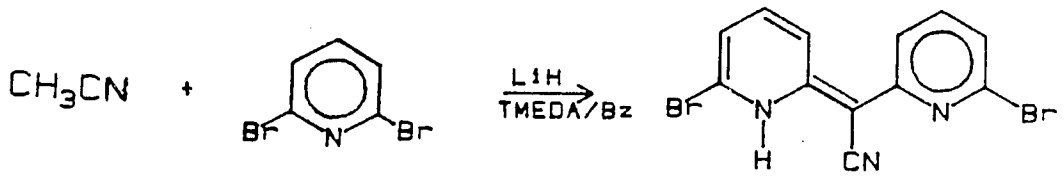
Sodium and lithium hydrides react slowly with active methylene compounds bearing *only one* electron-withdrawing group; thus application was limited to the alkylation of arylacetonitriles. However, since it was easier to handle these hydride reagents, relative to sodium amide, an excess of hydrides could be used to offset the diminished yields[136] of alkylated products. It is a general rule that application of LiH (NaH) to the alkylation of aliphatic acetonitriles leads to extensive polymerization[103] under the usual heterogeneous conditions.

In contrast to alkyllithiums, abstraction of a hydrogen from acetonitrile by LiH (NaH) in DMF at 25°C was not detected. At temperatures greater than 100°C, DMF with metal hydrides liberated dimethylamide, which attacked 2,6-dibromopyridine to give *N,N*-dimethyl—aminopyridines **136** and **137**, as well as traces of 122. The ^{1}H NMR spectrum of **136** exhibited a singlet at δ3.05 for the two methyl groups, two doublets at δ6.35 and 6.55 for 3- and 5-py*H*, respectively, and a triplet at δ7.23 for 4-py*H*. The MS data showed two peaks at m/e 202 and 200 for the molecular ions. Disubstituted **137** was confirmed (^{1}H NMR) by the singlet at δ3.02 for four methyl groups, a doublet appeared at δ5.80 for 3- and 5-py*H*, and a triplet at δ7.27 indicative of the 4-py*H*.



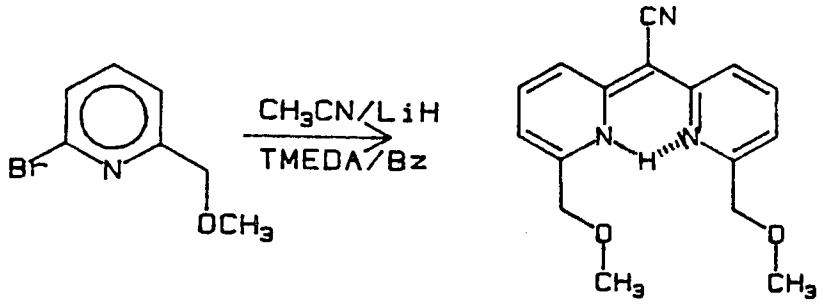
The use of 5% TMEDA/benzene solvent system prevented this side reaction and also stabilized lithioactonitrile. Another advantage of this co-solvent system is the easy control of temperature at 80°C. 2,6-Dibromopyridine with LiH and acetonitrile in 5% TMEDA/benzene was refluxed for two days to give (47%) the desired **122**, which was identified by its characteristic ^{1}H NMR spectrum consisting of a complex aromatic region as well as the broad singlet at δ16.0 for the bridging hydrogen atom. The ^{13}C NMR

spectrum of 122 appeared as typical seven signals including the methine carbon at δ64.5. The IR spectrum showed a conjugated nitrile absorption at 2200 cm^{-1}. The MS data were dominated by three peaks at m/e 355, 353, and 351 in a 1:2:1 ratio which corresponds to the isotopically different molecular ions.



122

Similarly, the reaction[137] between acetonitrile and 2-methoxymethyl-6-bromopyridine with LiH in 5% TMEDA/ benzene gave *bis*-2-(6-methoxymethylpyridyl)acetonitrile (165), as yellow needles. The ^1H NMR spectrum of 165 showed a characteristic broad singlet at δ16.4 indicative of the N-H••N interaction and two singlets at δ3.49 and 4.52 for OCH_3 and $pyCH_2$-O, respectively; in the aromatic region, a triplet of doublet at δ6.60 for 5-py*H*, a doublet at δ7.34 for 3-py*H*, and a triplet at δ7.56 for 4-py*H*. The MS data were



165

dominated by the parent peaks at m/e 284 and 283. Spectroscopic evidence agreed with tautomeric equilibrium in solution *via* N-H forming a bifurcated hydrogen bond.

The crystal structure[137] of 165 (Figure 10) confirms a fixed tautomer in the solid state; only one of the pyridyl units is protonated. The N-*H* [bond length 0.931(12)Å] forms a bifurcated hydrogen bond with H(N1)-N3 1.876(12)Å and H(N1)-O1 2.219(11)Å. The major features of this solid state conformation are described by several key torsion angles (Table A3). Torsion angles O1-C2-C3-N1 and N3-C14-C15-O2 are 6.7 and 175.7°, respectively, because of H-bonding H(N1)-O1 and non-hydrogen bonding H(N1)-O2. An average torsion angle of N1-C7-C8-C9 and N3-C10-C8-C9 is 179.1° indicating that the dipyridylmethine unit is nearly planar. The N1 pyridine forms dihedral angles of 4.9 and 1.6° with N2 pyridine and the best-plane of nitrile, respectively, which form dihedral angle of 3.4° with each other. Bond angles of C7-C8-C9, C7-C8-C10, and C9-C8-C10 are 116.8(1), 125.9(1), and 117.2(1)°, respectively. Bond lengths of C7-C8 [1.410(1)Å, methine to a protonated pyridine] are shorter than C8-C10 [1.452(1)Å, methine to an unprotonated ring]; however, both bond lengths are longer than double bonds (1.32Å)[138], but shorter than single bonds [C2-C3 and C14-C15 are 1.498(2) and 1.496(1)Å, respectively]. The intermediate bond lengths observed correlate with the chemical shift of the methine carbons, which appears at $\delta 70 \pm 6$ instead of falling within the double bond region (δ100-145).[139] A protonated pyridine ring is more distorted than the unprotonated counterpart; C3-C4 [1.357(1)Å]

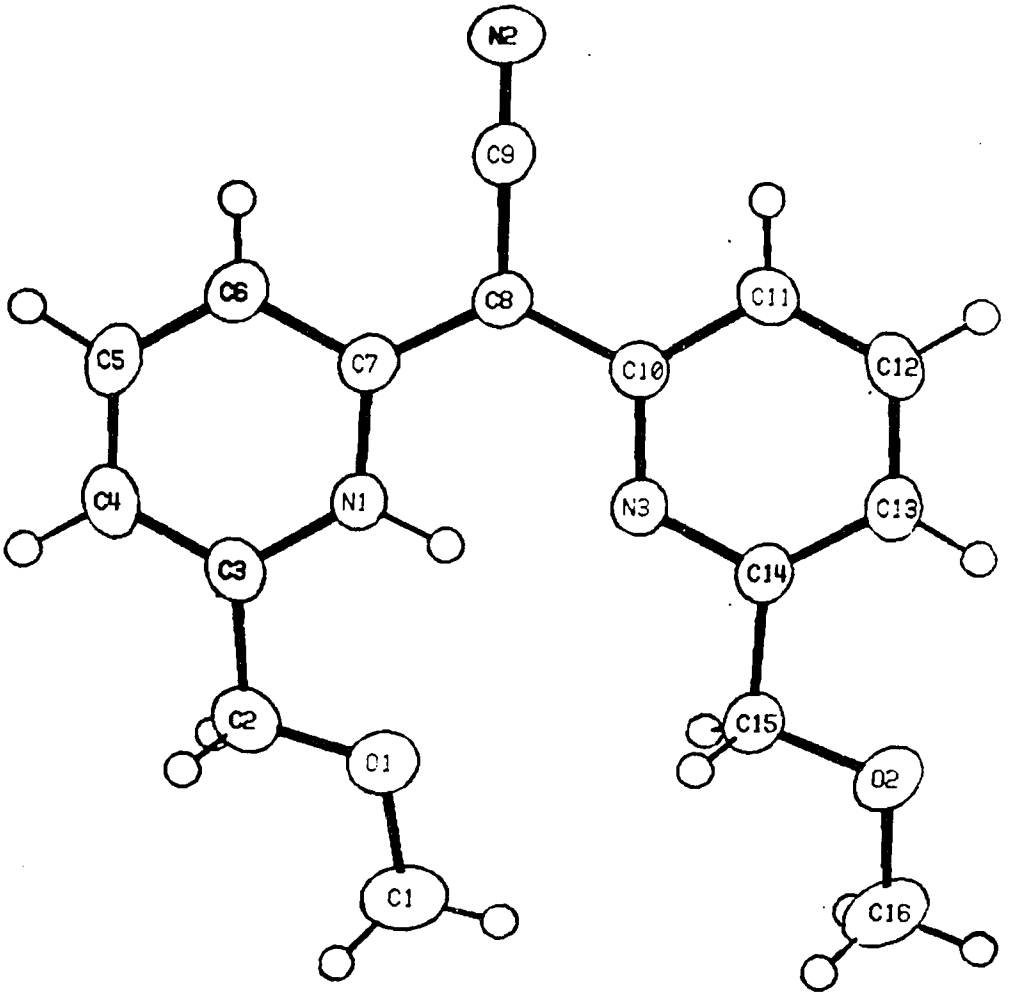
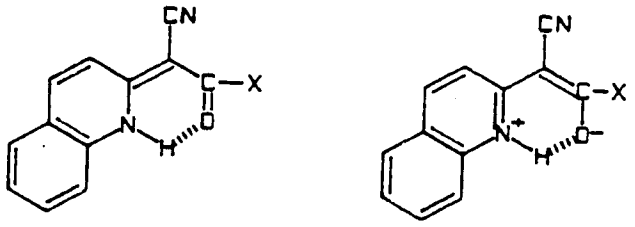


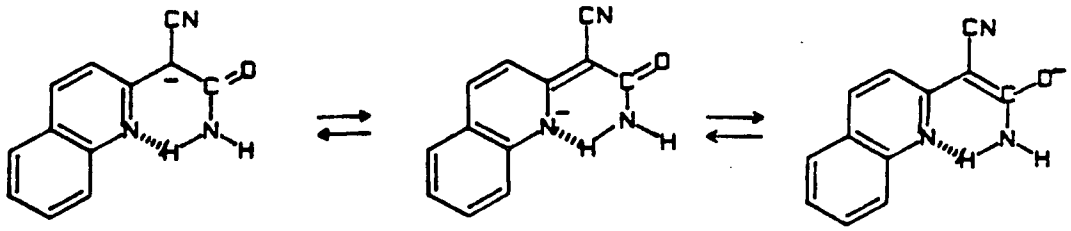
Figure 10. ORTEP of **165**.

and C5-C6 [1.350(1)Å] are shorter than the corresponding C13-C14 [1.382(1)Å] and C11-C12 [1.370(1)Å]. However, C4-C5 [1.400(2)Å] and C6-C7 [1.418(1)Å] are longer than C12-C13 [1.385(1)Å] and C10-C11 [1.401(1)Å], respectively. These bond length data corroborate the fact that the three shorter bond lengths (C3-C4, C5-C6, and C7-C8) have more double bond character than C4-C5, C6-C7, and C8-C10: C7-C8 and C8-C10 are 1.410(1) and 1.452(1)Å, respectively. Bond distances and bond angles are compiled in Table A1 and the nonhydrogen atom coordinates are listed in Table A2.

Using these X-ray data, we can predict that **158a** and **158b** will be too stabilized by *H*-bonding to react with 2-chloroquinoline; however, the alternate hydrogen bonding options with amido NH_2 in



158a, X = O-t-Bu
158b, X = O-Et



159b **159a** **159c**

intermediate **159a-c** increase the electron density on the methine carbon sufficiently to facilitate attack on 2-chloroquinoline, which lead to the formation of **160**.

Characteristic features of these *meso*-cyanides (quinolylmethanes) are illustrated at Table 2. Their IR spectra display a conjugated nitrile absorption in the general range of 2160-2200 cm^{-1}. Direct spectroscopic evidence for a N-H••N bond is confirmed (^1H NMR) by a broad singlet at $\delta 15.7 \pm 0.8$ ($CDCl_3$). The ^{13}C NMR spectra of these methine-bridge sp^2-carbon atoms display signals in

Table 2. Characteristic Physical Data for *Meso*-cyanides

compd	IR(cm^{-1}) for C≡N	^1H NMR (NH)	^{13}C NMR [C(sp^2)]	M.P. (°C)
95[100]	2180	----	----	>400(dec)
122	2200	16.0	64.5	163-164
124	2162	16.5	69.0	268-269
127	2190	15.0	70.4	390(dec)
128	2190	16.3	67.5	129-130
	----	16.1[113]	----	129
129	2185	15.1	68.4	157-158
134	2180	15.8	75.5	246-248
135	2190	15.6	----	255-257
160	2200[132]	----	----	284
	2170[140]	----	----	281-283
165[137]	----	16.4	----	---

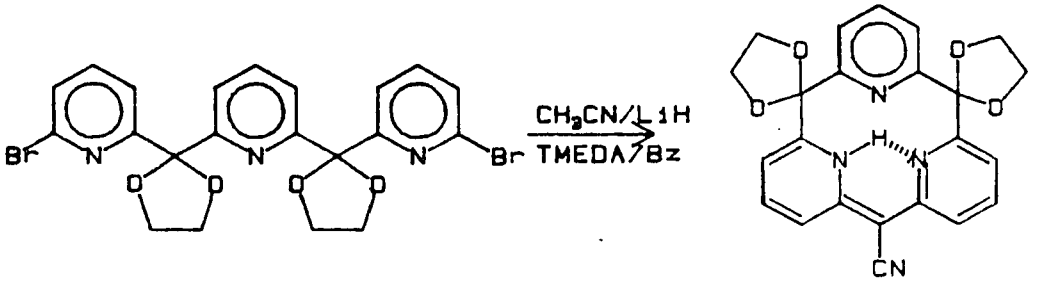
the region of $\delta 70 \pm 6$; bond angles around the bridges are ca. 120°, however, the average bond lengths (ca. 1.43Å) longer than those for normal sp^2 bonds. Typically, high melting points are observed compared to structural counterparts. The low solubility of *meso*-cyanides in common organic solvents makes purification and characterization difficult but is consistent with the properties expected for the dominant highly polarized structures.

VII-3. Cyclization to Form [1_3](2,6)Pyridinophanes

In analogues of porphyrins, trione **115** is the simplest member of *C*-bridged, electron-deficient series and thus should be the ideal structure to probe the electronic and/or steric effects of the directed *N*-electrons within a highly rigid cavity, as well as being ideally suited to be the perfect proton sponge. Previous, a low-yield route to **115** *via* a low-temperature (-100°C), nucleophilic substitution[118] provided very limited samples for characterization. The inability to cyclize the intermediates was attributed to unfavorable conformational orientations at these reaction temperatures.

In order to facilitate cyclocondensation, the reaction of **123** with lithioacetonitrile, generated from anhydrous acetonitrile in 5% TMEDA/benzene with LiH, was conducted at 80°C. This mode of cyclocondensation was successful owing to the elevated reaction temperatures and metal ion templation, which are both favorable to product formation.[141] Thus, refluxing the mixture for 2 days under

an inert atmosphere produced, after hydrolysis, a yellow, crystalline macrocycle **124**, which contains both ketal and nitrile functionalities. The facile macrocyclization probably resulted from the ability of the *N*-electrons to coordinate lithium, thus forming an intermediate complex to ensure the proper juxtaposition of the termini.



123 **124**

The ^{1}H NMR spectrum of **124** showed a broad singlet at δ16.5 indicative of a N-*H*••N. A complex pattern was centered at δ4.26 for the ketal hydrogens; this was probably due to their non-equivalence suggestive of a nonmobile conformation within the framework. A complicated pattern was also shown at δ6.96-7.86 for the remaining pyridyl hydrogens since all the positions were unique (no symmetry mirror planes). The ^{13}C NMR spectrum of **124** confirmed the C_2 symmetrical cyclic structure, in which only eight pyridine carbons appeared in the aromatic region. The methylene (δ65.9), methine (δ69.0) (see Chap. VII-2), ketal (δ104.9), and nitrile (δ122.6) carbons all appeared in the predicted locations. Other characteristic features of **124** were the high melting point

(268-269°C) relative to trione **115** (236.0-236.5°C) and the spike at $2162cm^{-1}$ in IR spectrum for the conjugated nitrile.

It was essential that the structure of this pivatol intermediate be established; Figure 11 illustrates the crystal structure of **124**. The fixed tautomeric form in the solid state, the bifurcated *H*-bond, the key bond lengths [0.86Å for H-N1 (d^1), 2.16Å for H(N1)-N2 (d^2), and 1.96Å for H(N1)-N3 (d^3) (Table A4)] confirm the cyclic structure. Half of the hydrogens were observed as N1-H bond, and the remaining hydrogens formed N3-H bond with an equivalent bond length. This observation can be attributed to either a statistical distribution of NH tautomers in the crystal or to rapid interconversion of the tautomers during the time required for measurement.[72] Bond lengths of C1-C18 and C17-C18 are both 1.431(2)Å and the dipyridylmethine moiety is nearly planar with maximum deviation from planarity of 0.118(2)Å (for N1). The central pyridine formed a dihedral angle of 70.9° with this plane; whereas, N2 is nearly coplanar [deviation 0.066(2)Å] with the dipyridylmethine, and the N1-N2 and N2-N3 bond distances are 2.807(2) and 2.643(2)Å, respectively. The two dioxolane rings are nonplanar and all of the atoms are twisted to the *opposite* side of the N2 pyridine.

Macrocycle **124** was the ideal precursor to the desired carbonyl bridged macrocycle **115**. The conditions necessary to convert both ketal and nitrile functionalities to ketonic moieties were tested with the model **122**. The nitrile group of **122** was removed under acidic conditions to afford (81%) **139**, as colorless needles. The

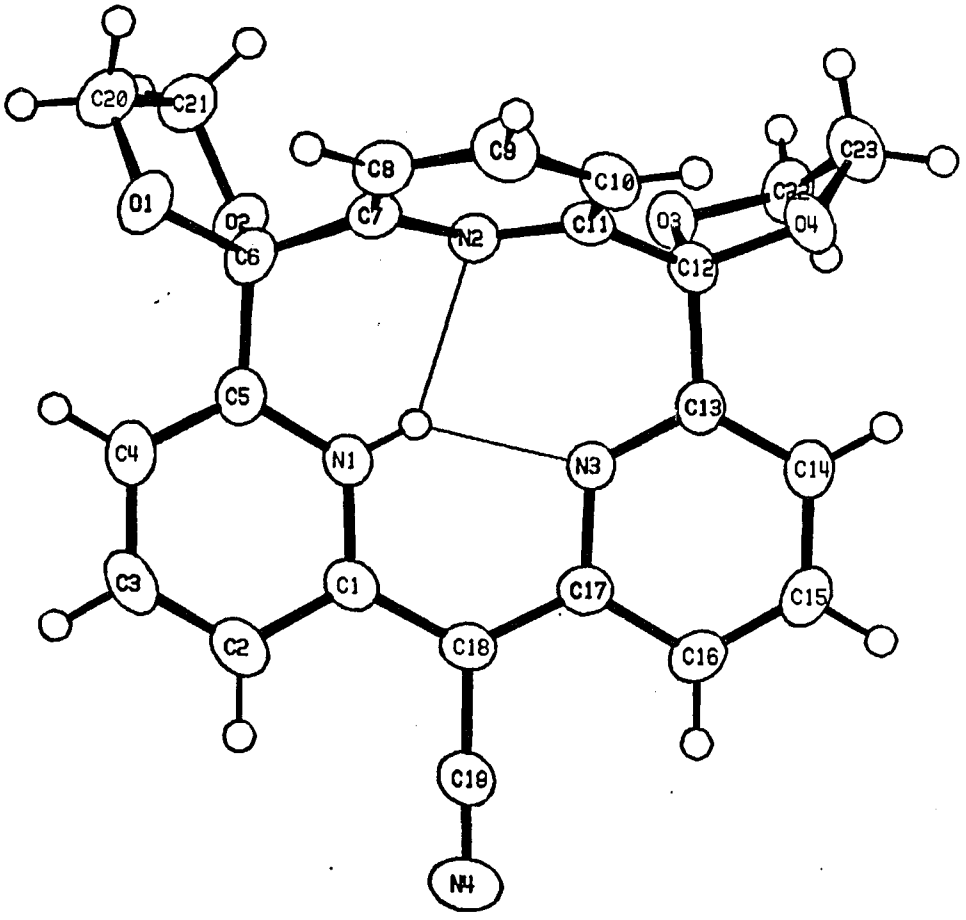
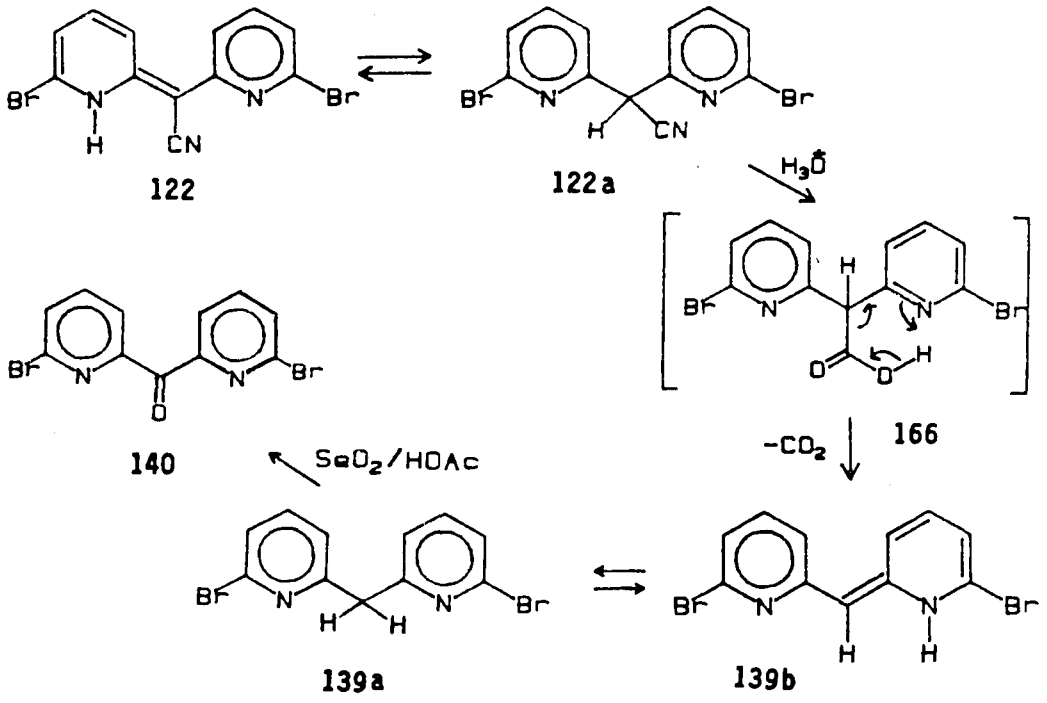


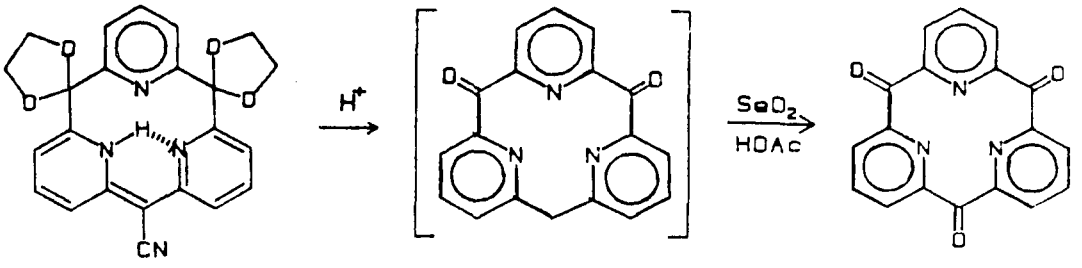
Figure 11. ORTEP OF **124**.

process was monitored by the appearance (^{1}H NMR) of a spike at δ4.27 for the *free* methylene confirming its selective generation. A possible cyanomethylene transformation can be envisioned to proceed through intermediate **166** from tautomer **122a**. Decarboxylation, which is known to proceed by a six-centered transition state,[142] generates **139a**. Subsequent oxidation[143] of the CH_2 to desired ketone in **139** was accomplished with SeO_2 in glacial acetic acid to give (72%) the known *bis*-2-(6-bromopyridyl)ketone (**140**).[118,119,121c,g]



Macrocycle **124** was hydrolyzed with EtOH/concd HCl (1:1, v/v) to give (80%) the unstable dione **143**, as a white solid. The ^{1}H NMR spectrum of **143** showed a complex aromatic region as well as the singlet at δ4.37 for methylene protons. This interpretation was corroborated by the MS data which exhibited a parent ion at m/e 301

(M^+, 100). Upon attempted purification, intermediate **143** decomposed by facile self-dimerization; details of dimerization process are reported in Chap. VII-5.



124 **143** **115**

Crude **143** could be oxidized with SeO_2 in glacial acetic acid to afford in high yield the desired trione **115**, as pale yellow crystals. The symmetric structure of **115** was initially confirmed by its exceedingly simple ^1H NMR spectrum; a doublet of doublets at δ8.12 ($J_{3,4}=J_{4,5}=$ 7.9Hz) for 4-pyridyl hydrogen and a doublet at δ8.34 for 3,5-pyridyl hydrogens. The simple AB_2 pattern unequivocally demonstrated the high degree of molecular symmetry that would be expected for such a cyclic molecule. Further evidence of the gross structural assignment was provided by ^{13}C NMR data, which showed *only* four peaks at δ126.7 (*C*3), 138.0 (*C*4), 152.9 (*C*2), and 188.1 (*C*=O). The high melting point (236.0-236.5°C) and meager solubility in common organic solvents were also indicative of the symmetric nature of **115** as well as the effect of pyridino subunits. Very similar properties are exhibited by known calixarenes.[24,52,54,55]

The mass spectrum of **115** showed an anticipated molecular ion at m/e 315. The carbonyl group (IR) appeared at 1667cm^{-1} and was quite distinct from *bis*-2-(6-bromopyridyl)ketone (**140**)[121c,d] (1690cm^{-1}). This notable shift (ca. 23cm^{-1}) further supports the *syn*-conformation in **115**; the *anti*-conformation of two pyridyl nitrogens in **140** was, of courses, not possible for macrocycle **115**. Small crown ethers, which possess *bis*(2-pyridyl)ketone subunit, also have the carbonyl absorption in the same range (1666-1682cm^{-1}).[121g] These spectral data support a structure with a high degree of molecular symmetry (C_3) for trione **115**, at least within the NMR time scale. The crystal structure was deemed essential to confirm the structure and to furnish some insight into the critical molecular deformation caused by the juxtaposed *N*-electrons within the core.

For the X-ray structural analysis, trione **115** was recrystallized from methanol. Initial refinement of the X-ray data suggested that the crystal did *not* possess the desired symmetry for the proposed trione **115**. Detailed analysis showed the crystals to be hemiketal **167**, which arose from the unexpected, but yet easy, conversion of **115** to **167**, during recrystallization. This hemiketal was asymmetric as illustrated in Fig. 12. The molecular structure of **167** was shown to be severely distorted from planarity since the two nitrogens (N1 and N2) tip out-of-the-plane on *one side of the molecule*, and the other nitrogen (N3) tips in the opposite direction. Thus, the three pyridines staggered between two carbonyl planes; however, hemiketal formation occurs at the

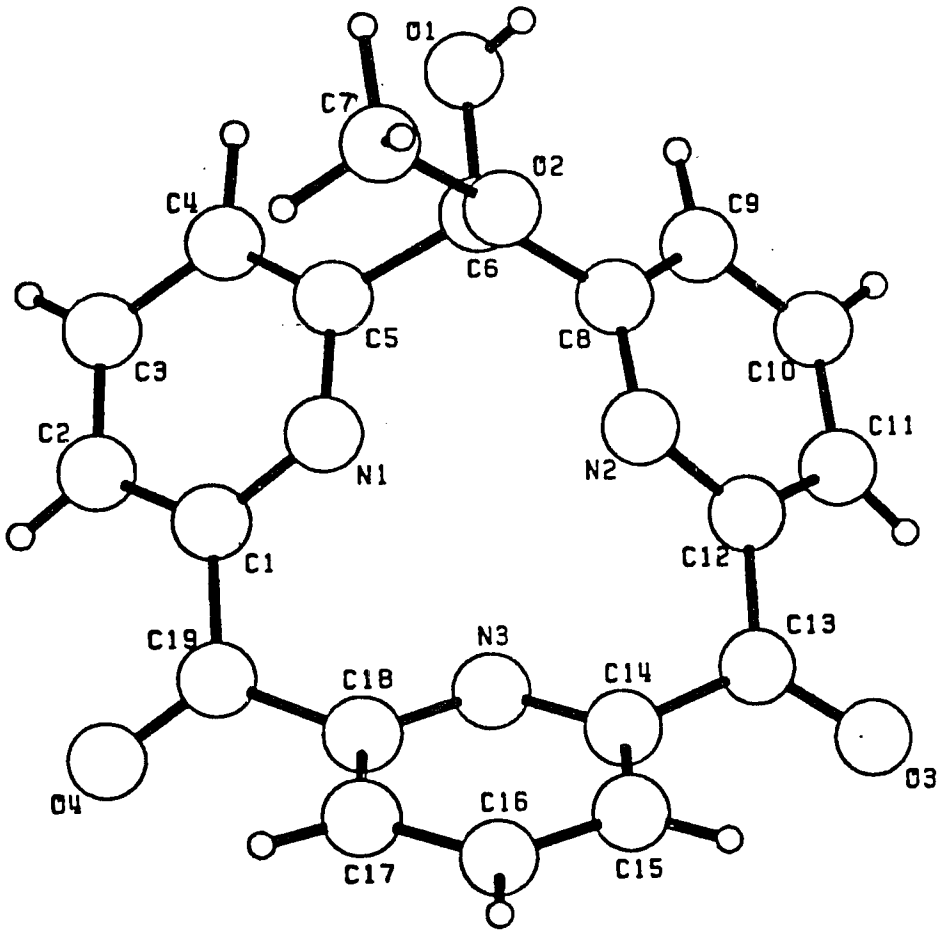


Figure 12. ORTEP of **167**.

carbonyl when two pyridine rings were *syn* disposed, forcing repulsion between two *N*-lone pairs. Bond distances and angles of **167** are compiled in Table A6; nonhydrogen atom coordinates are listed in Table A7.

In order to prevent hemiketalization of trione **115**, EtOH was diffused into $CHCl_3$ solution of **115** at 25°C. Slow evaporation of $EtOH/CHCl_3$ afforded *colorless*, transparent crystals of **115**. The X-ray crystal structure of **115** (Fig. 13) shows a distinctly nonplanar conformation in the solid state, contrary to the conclusions derived from solution studies, from molecular models, and from simple MO calculations. Distortion from planarity leads to a conformation with approximately C_s symmetry, in which two *N*-lone pairs (N2 and N3) are tipped out-of-the-plane on *one* side of the molecule, and the third (N1) is tipped in the *opposite* direction. A local mirror plane bisects both both N1 and opposite carbonyl (C12-O2). The N1 pyridine forms dihedral angles of 46.5° and 41.4° with the N2 and N3 rings, respectively, which form a dihedral angle of 35.4° with each other. The heteroaromatic *C-C* distances average 1.380(7)Å, *C-N* distances average 1.335(4)Å; whereas the C=O distances average 1.218(2)Å. Trione **115** contains only sp^2 ring atoms and should be essentially flat - barring any direct *N*-electron interactions. In conclusion, *the observed deformation from planarity must be predominately due to N-N-lone pair repulsion within confines of the cavity.*

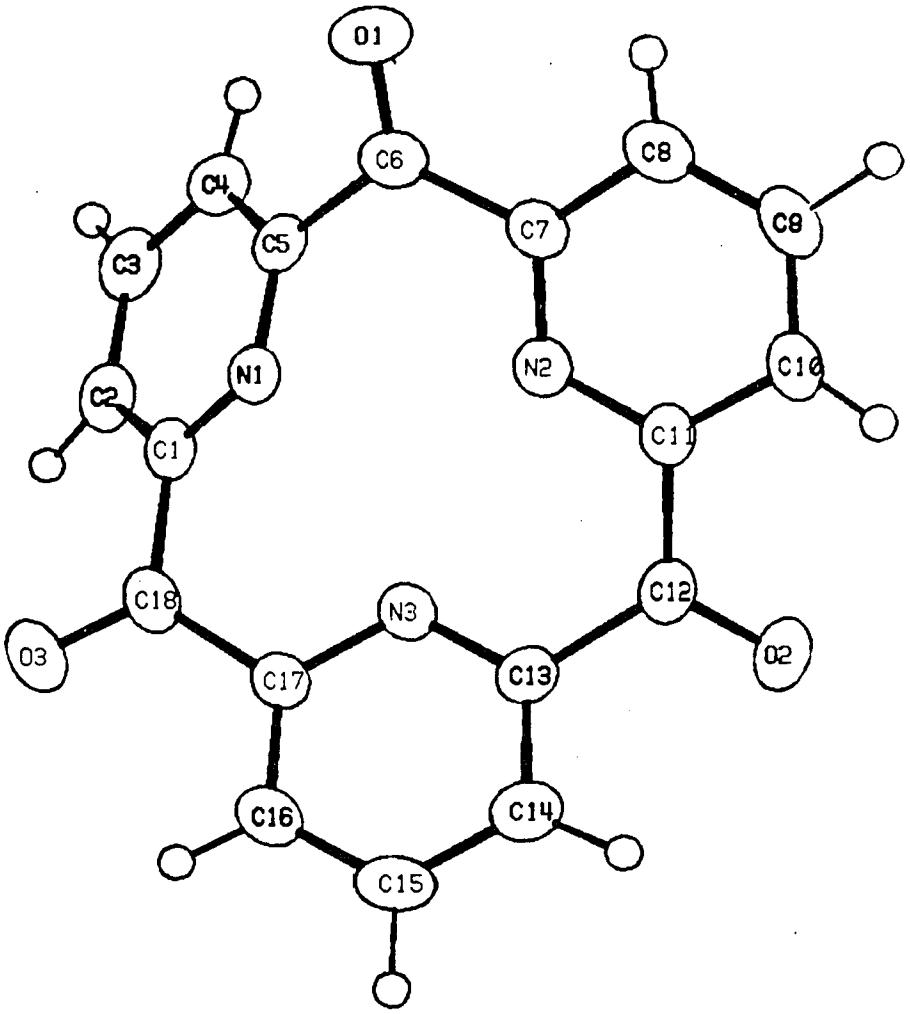
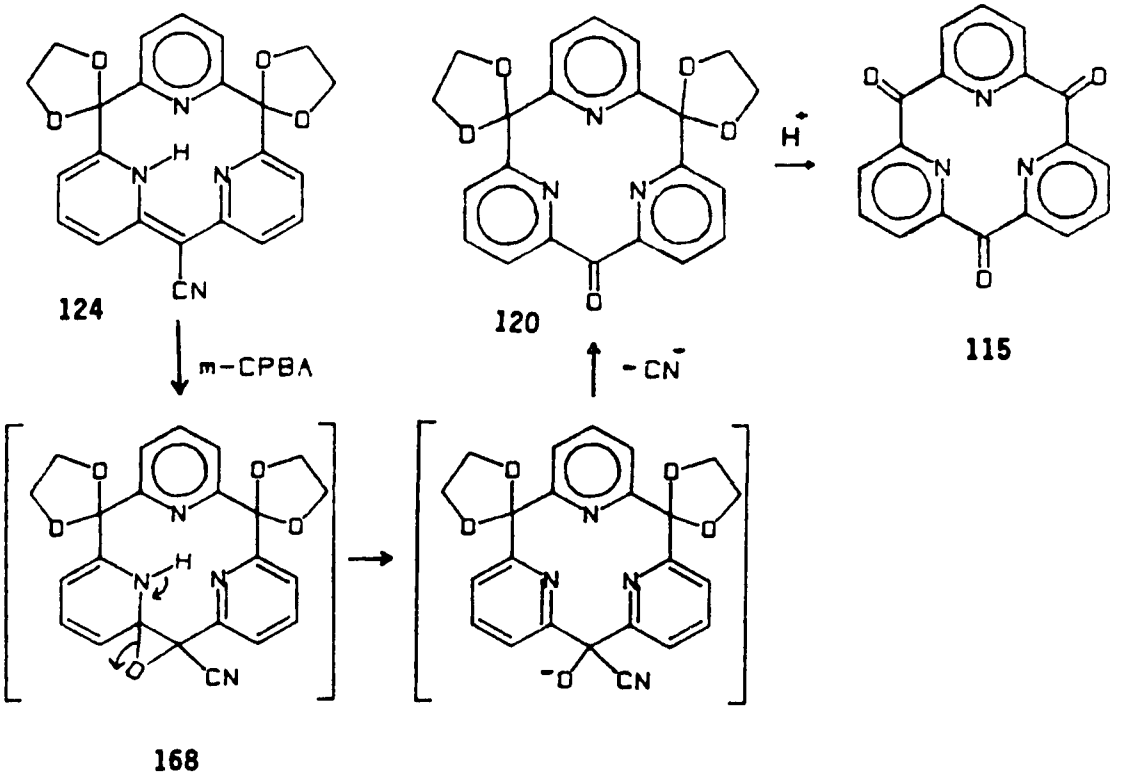


Figure 13. ORTEP of 115.

Another deprotective route (**124** to **115**) was designed in which oxidation of precursor **124** formed **120**, which was subsequently deketalized under acidic conditions. The oxidation of **124** with *m*-chloroperbenzoic acid[144] afforded (68%) diketal **120** *via* an initial facile epoxidation of the exocyclic double bond to afford intermediate **168**, which underwent rapid explusion of CN^- to generate diketal **120**. The ^1H NMR spectrum of **120** exhibited a singlet at δ4.24 for the two ketal methylenes as well as a complex aromatic region. No evidence of conformational changes in the



low-temperature (220K) ^{1}H NMR spectrum of **120** was observed even through there must be considerable flexibility of the pyridine rings as determined by X-ray analysis of **115**. Supportive ^{13}C NMR spectrum showed eleven signals and the MS data exhibited fragments at m/e 404 (M^{+}+1, 20) and 403 (M^{+}, 83) for the parent ion.

X-ray diffraction data of **120** revealed the presence of two independent conformers (Figure 14 and 15). In both cases, the three pyridine rings deviated more from coplanarity than those of trione **115** at least in the solid state. The N1 (N1′) pyridine formed dihedral angles of 125.6° (92.5°) and 50.2° (45.8°) with the N2 (N2′) and N3 (N3′) rings, respectively, which form a dihedral angle of 104.8° (126.6°) with each other. The major features of its solid state conformation are described by several key torsion angles for a given isomer. Torsion angles C18-C1-C2-N1 [43.7(4)°], N1-C6-C7-C8 [-51.6(4)°], N2-C12-C13-C14 [62.3(3)°], and C12-C13-C14-N3 [-65.4(3)°] for Conformer 1 indicate that all of the three *N*-lone pairs are *not* directed to the cavity (Table A14); two nitrogens (N2 and N3) are tipped out-of-the-plane on one side of the molecule, and the other nitrogen is tipped in the opposite direction.

Diketal **120** was deprotected with concentrated HCl to give (60%) trione **115**. This approach simplified the isolation procedure, since it was not necessary to remove Se° and HOAc associated with the SeO_2 oxidation in the first procedure.

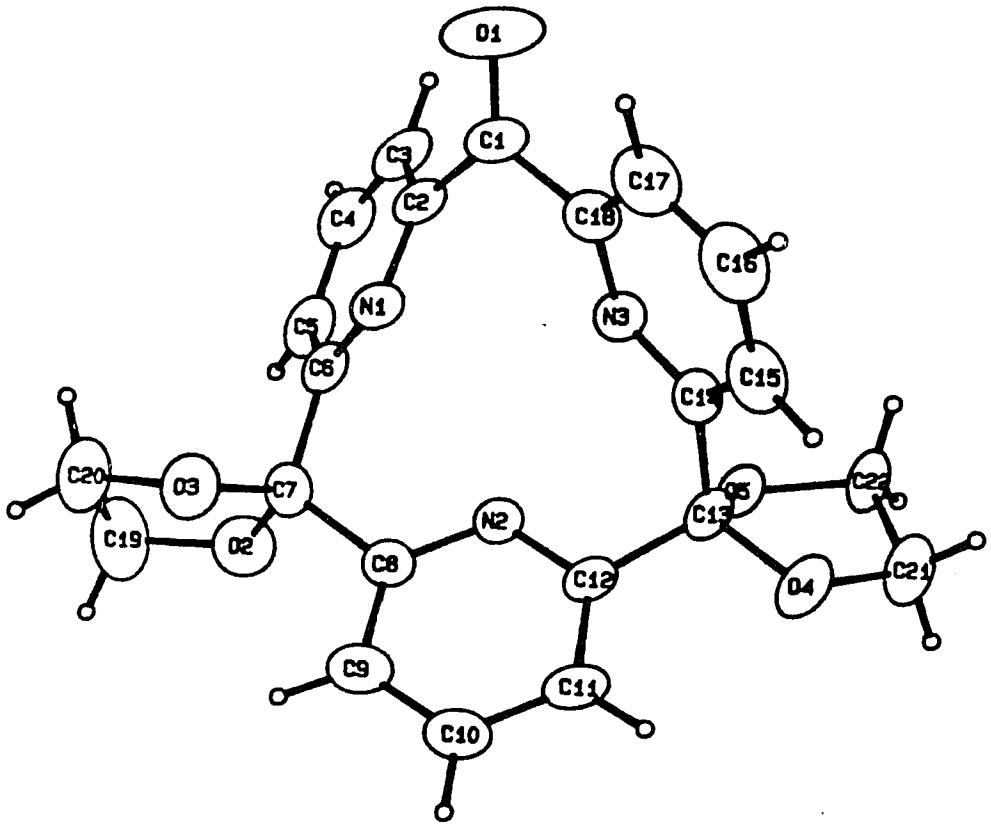


Figure 14. ORTEP of 120 (Conformer 1).

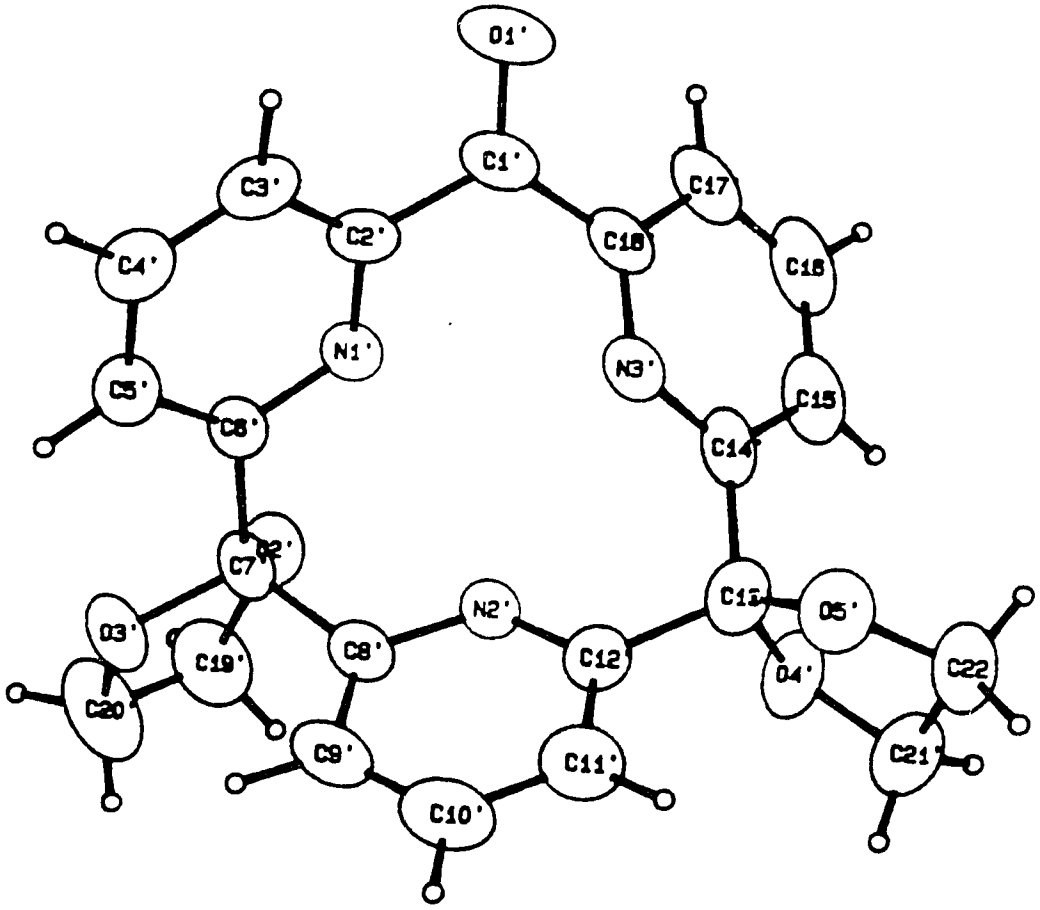
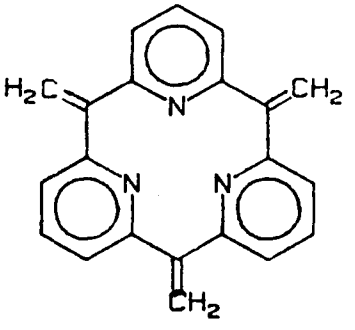


Figure 15. ORTEP of 120 (Conformer 2)

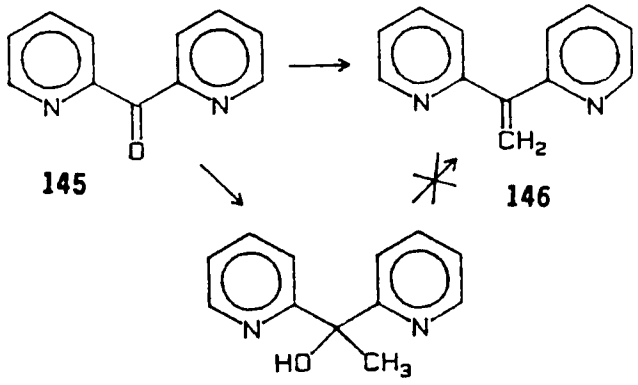
VII-4. Modification of Trione 115

Preliminary studies were undertaken on the alteration of a carbonyl moiety in order to establish the necessary ground-work for controlled *N*-electron density within the macrocyclic core. These preliminary studies, illustrated below, were limited to the chemical modification of the carbonyl group(s) by "exchange" for an exocyclic methylene group. This modification was deemed to be important since it would drastically enhance the *N*-electron density within the cavity. Since the *N*-electron density and thus orbital size are determined by the degree of electron-withdrawal from the heteroaromatic ring, removal of the carbonyl functionality should make a significant impact upon the electron density. The carbonyl group is a classic example of an electron-withdrawing substituent; thus its transformation to an alkene moiety would minimize the positive charge on the bridging carbon and increase the cavity's *N*-electron density while still retaining the structural integrity. Traditionally, the Wittig reagent, derived from methyl (or alkyl)-triphenylphosphonium bromide,[127] could effect this transformation.



169

The model substrate selected to evaluate known Wittig procedures was *bis*(2-pyridyl)ketone (**145**). Preparation of 1,1-di-(2-pyridyl)ethene (**146**) was attempted by three routes. In Method A, *n*-BuLi in ether was used to abstract the acidic hydrogen of methyltriphenylphosphonium bromide: basically the mixture was stirred at -70°C for 30 minutes, then **145** was added. After work-up, the desired **146** was isolated (10%) along with predominately unchanged starting ketone. In Method B sodium methylsulphinyl carbanion[128] was substituted for the butyllithium; the yields were again meager (10-17%), and major difficulty was encountered with isolation of pure **146**. The structural assignment of **146** was made on the strength of the characteristic ^{1}H NMR signal for the 1,1-disubstituted olefin, in which the $=CH_2$ signal was observed[126] as a singlet at δ6.05.

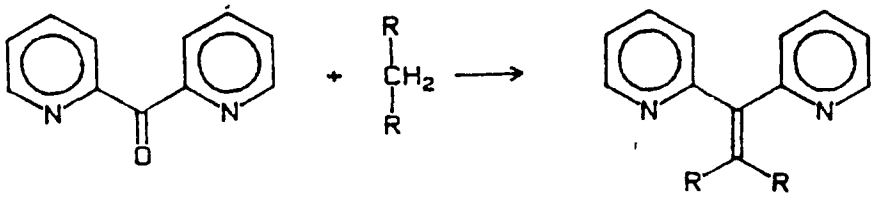


145 **146** **147**

In light of the low yields, an alternate route to **146** was explored (Method C), in which alcohol **147** would be dehydrated. Since precursor 1,1-di(2-pyridyl)ethanol (**147**) was known[129] and

readily available, its dehydration[127] in refluxing 80% H_3PO_4 was attempted. After work-up, only unchanged **147** was isolated (>70%) along with unidentified intractable resins.

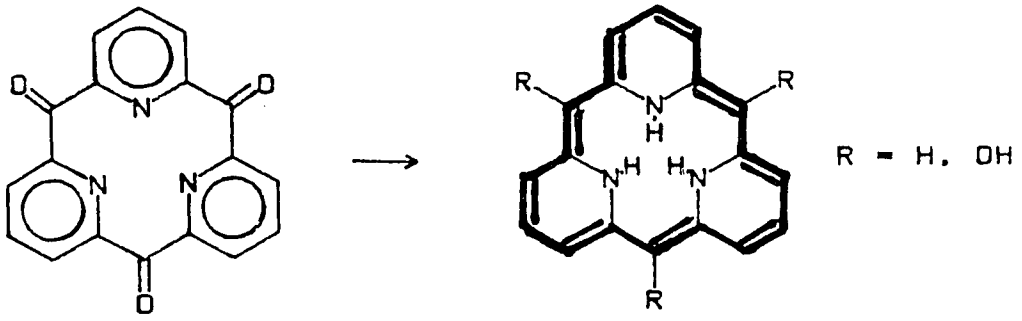
In conjunction with the synthesis of exocyclic methylene groups, numerous routes have been attempted.[145] Classically, condensation of aldehydes or ketones with active methylene compounds in the presence of amines,[146] known as the Knoevenagel condensation,[147] has been used. Thus, *bis*(2-pyridyl)ketone (**145**) with diethyl malonate (R = CO_2Et) or malononitrile (R = C≡N) should afford tetrasubstituted ethylenes **170**. An equimolar mixture of **145** and diethyl malonate (or malononitrile) in dry benzene with ammonium acetate in glacial acetic acid, as a catalyst, was refluxed, and water was removed from the azeotrope using a Dean-Stark separator. After ca. three days, the mixture was cooled and worked-up by general procedures. Only an ill-defined, intractable resin was isolated; no ethylenic products were isolated.



145 R = CO_2Et, CN **170**

Reduction of **115** was designed to afford 1,5:7,11:13,17-triepimino[18]annulene (**171**), whose gross structure possesses a peripheral *C18*-conjugated system. This annulene should be almost

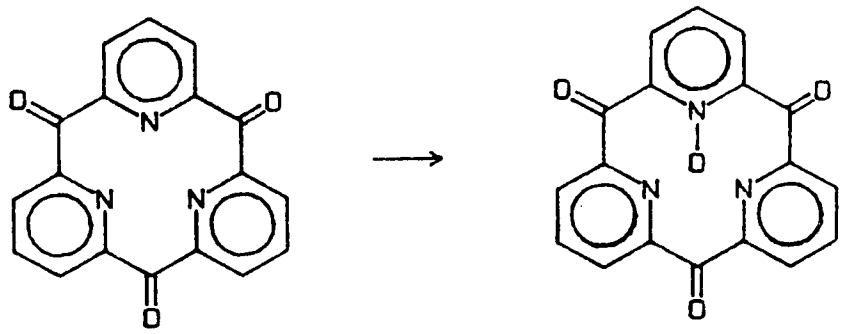
strainless although the three nitrogen hydrogens will most assuredly be displaced above and below the molecular plane. This *C18*-annulene should also possess benzenoid character, based on the Hückel 4n+2 rule,[148] if the deviation from planarity is slight.



115 171

When **115** was treated with BH_3, either at -70°C for two hours then a warm-up period, or at -70°C for three days, the results were essentially identical. In addition to unchanged **115**, unknown polymers were produced.

In the hopes of generating the model *N*-oxide **172** which could imitate hemoglobin action as oxygen carrier (**115**·O_3) and/or singlet oxygen generator, trione **115** was treated with *m*-chloroperbenzoic acid in $CHCl_3$ and refluxed. After work-up, only unchanged **115** was

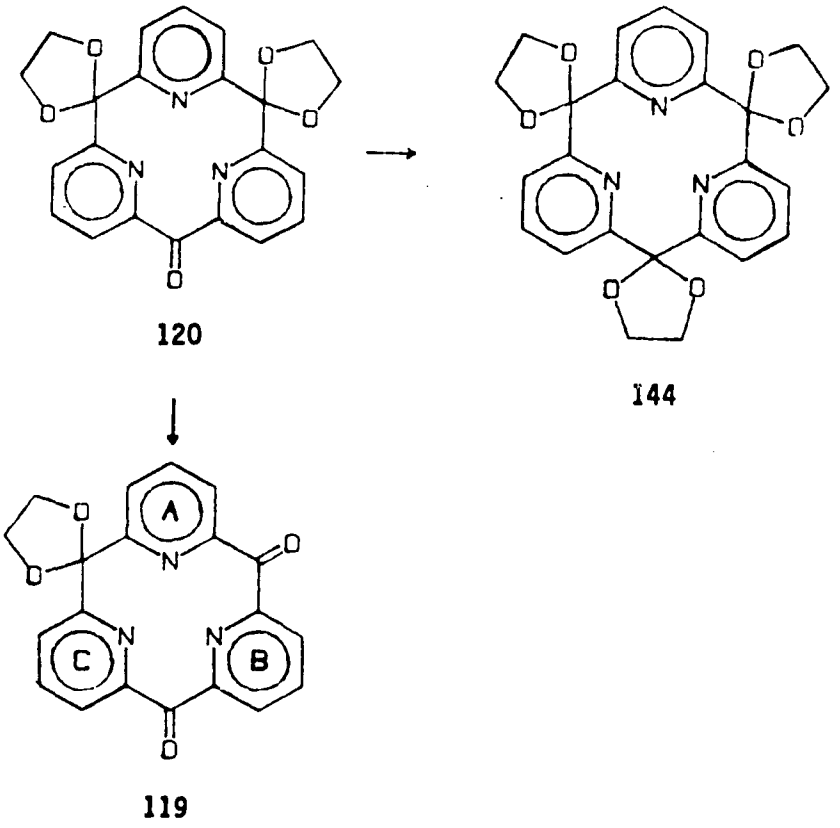


115 172

identified by ^1H NMR; however, the MS data exhibited a *low* intensity peak at m/e 331, attributable to 172. When 115 was reacted with H_2O_2 in glacial acetic acid, unchanged 115 was also isolated along with unidentified heteroaromatics, which were assigned as linear materials *via* the Baeyer-Villiger oxidation.[149]

The electronic repulsion and/or ring strain within the cavity of trione 115 was the rationale offered for the facile formation of hemiketal 167. This hemiketalization was also observed when trione 115 was complexed with Cu(II) in EtOH/$CHCl_3$ (CHAP VII-7). Diketal 120 has two protected bridges and one free carbonyl group, which leads to less ring strain, based on CPK models. Thus, triketal 144 should have the least ring strain in this series. The current availability of 120 made the preparation of 144, a straightforward matter. Upon ketalization of 120 under acidic conditions, the triketal 144 was isolated (≥40%) and shown to be extremely insoluble in most common organic solvents (e.g. $CHCl_3$, DMSO, MeOH, and EtOH). The ^1H NMR spectrum of 144 showed a singlet at δ4.27 for the methylenes and a complicated pattern between δ7.71-7.93, which integrated to nine hydrogens. This interpretation was corroborated by the MS data, which exhibited peaks at m/e 448 (M^++1, 10) and 447 (M^+, 39) for the desired molecular ion.

Partial deketalization of 120 with alcoholic HCl gave (54%) the monoketal 119, as colorless needles. The ^1H NMR spectrum of 119 exhibited a singlet at δ4.30 for the methylenes and multiplet at δ7.84-7.98 for the A and C pyridines. A triplet at δ8.04 and a doublet at δ8.28 for the pyridine ring flanked by the carbonyl



groups are nearly identical to the pattern for **115**, as would be expected. Figure 16 illustrates the crystal structure of **119**, which is very similar to that of hemiketal **167**. The N3 pyridine forms dihederal angles of 40.0° and 42.2° with the N1 and N2 rings, respectively, which form a dihedral angle of 78.2° with each other indicative of N1 ring tipping out-of-the-plane on one side of the molecule, and the other pyridine rings (N2 and N3) tip in the opposite direction. Average torsion angles of two C=O to pyridine plane are 26.2°, but N2-C11-C12-C13 and C11-C12-C13-N3 are 70.3(4)° and -63.6(5)°, respectively (Table A17). The pyridine rings (N2 and N3) are turned with respect to the dioxolane ring such that

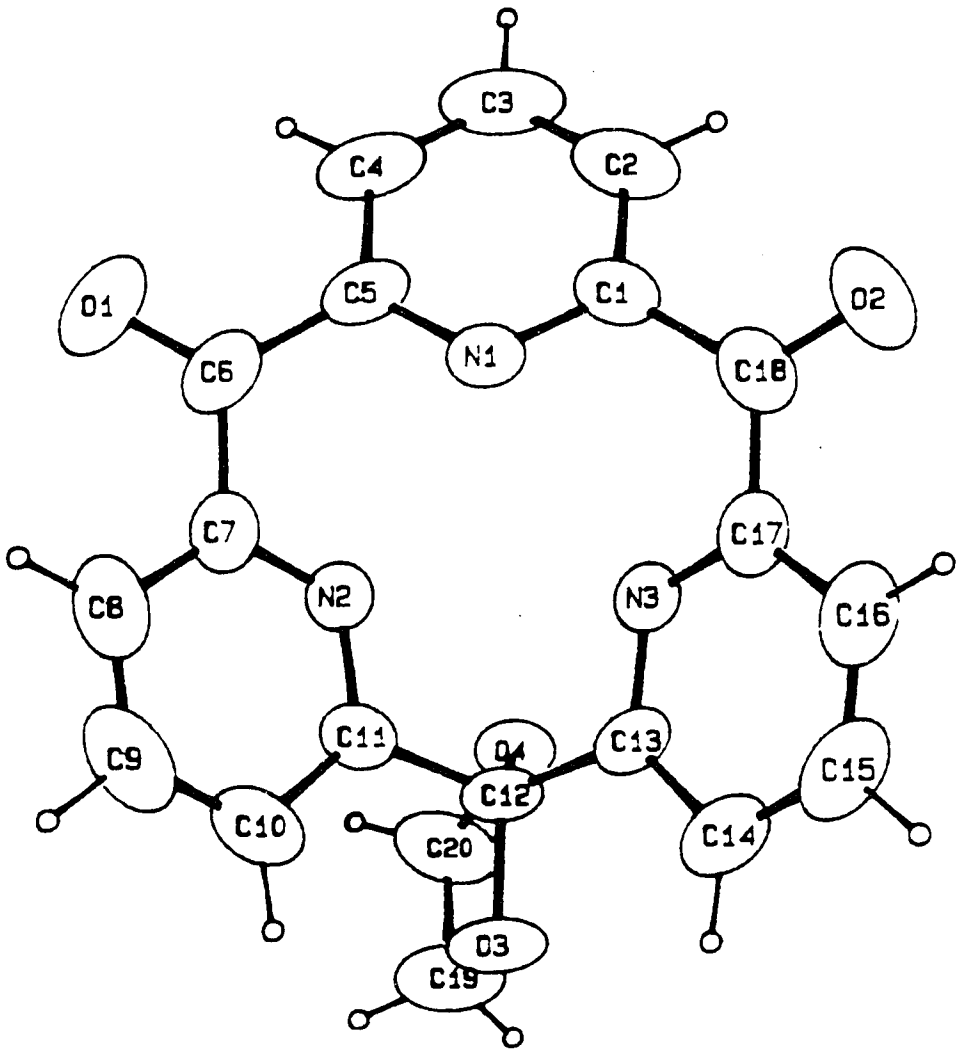


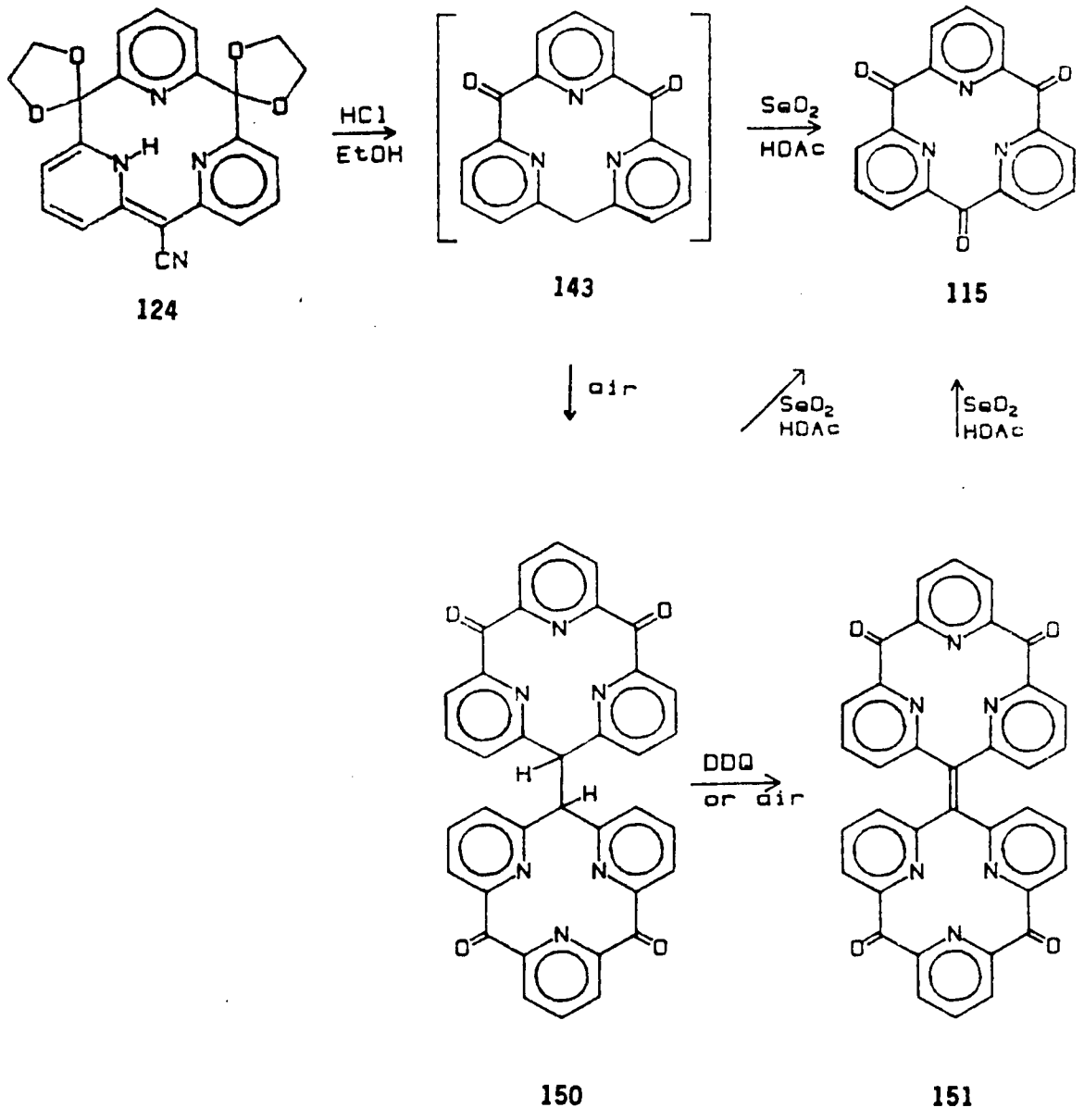
Figure 16. ORTEP of 119

the nitrogen atoms are essentially *anti* to oxygen O3; the dihedral angle of pyridine rings between dioxolane is 101.8°. This conformational structure of **119** is also similar to that of diketal **120**, in which the two pyridines about carbonyl are twisted.

VII-5. Self-dimerization of 143 and Dehydrogenation of its Dimer (150)

One of the most interesting features of **143**, which contains one methylene and two carbonyl bridges, was the high reactivity of methylene hydrogens towards oxidation. When **124** was deprotected with EtOH/HCl under an inert atmosphere (Chap. VII-3), crude **143** was isolated (81%) as a white solid. The ^{1}H NMR spectrum of **143** exhibited a singlet at δ4.37 for methylene protons as well as a complex aromatic region. This interpretation was corroborated by the MS data, which showed a parent ion at m/e 301 (M^+, 100). When **143** was purified by column chromatography on silica gel, a dimer **150** (31% from **124**) was obtained, as colorless needles. This easy dimerization was unexpected but suggests that the methylenic hydrogens are easily lost as hydrogen atoms under aerobic conditions.

The ^{1}H NMR spectrum of **150** supported the symmetric structure. (Fig. 17) The equivalent ethane hydrogens appear as a singlet at δ5.66 indicative of C-C bond formation and molecular symmetry. The aromatic region, although complicated, showed the 3-py*H* resonance at δ7.02 (dd, J=7.5, 1.1Hz), which was shifted up-field relative to



124 143 115

150 151

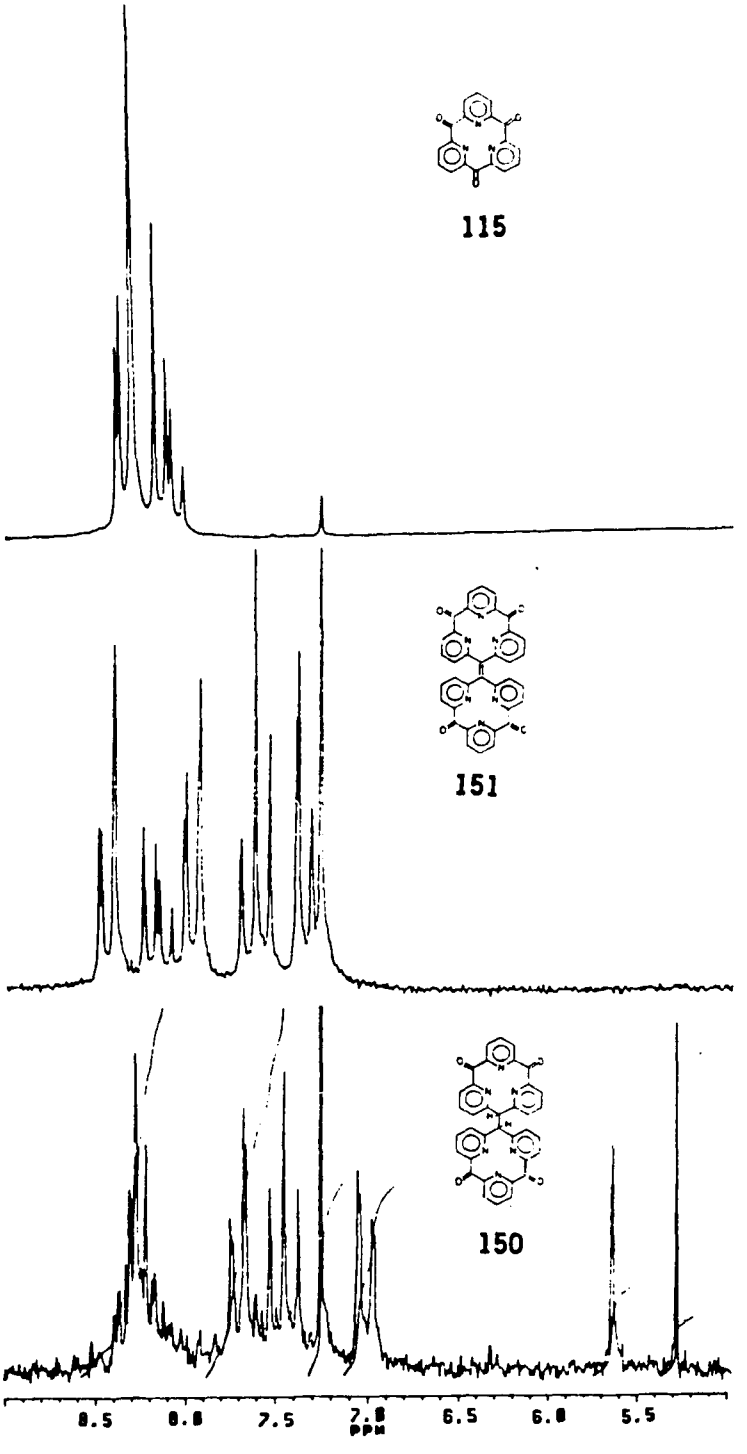


Figure 17. ^{1}H NMR spectra of 115, 150, and 151.

4-py*H* at δ7.46 (t, J=7.5Hz); whereas, the 5-py*H* appeared at δ7.71 (dd, J=7.5, 1.1Hz), which is a downfield shift relative to 4-py*H*. The complex pattern between δ8.13-8.40 is assigned to the remaining 3′,4′,5′-py*H*. The ^{13}C NMR spectrum of **150** confirmed the C_2 symmetry, in which *only* ten carbons appeared *including* the bridging sp^3 carbon at δ41.1 and the single carbonyl carbon at δ187.9. This interpretation was again corroborated by the MS data which exhibited a parent ion at m/e 600 (M^+, 77).

The crystal structure of **150** consists of two independent conformers, each lying on a center of symmetry (Fig. 18 and 19). Structural differences are small but notable. Each tripyridino subunit has the conformation seen in the analogous trione **115** with two *N*-lone pairs tipped out-of-the-plane on one side, and the third tipped on the opposite direction, yielding local C_s symmetry. In this case, the approximate mirror of this subunit is also a pseudosymmetry element of the entire molecule, which has overall local symmetry C_{2h}. Pyridine rings containing N1, N2, and N3 form diheral angles with each other: N1/N2 37.7°, N1/N3 75.3°, N2/N3 41.7°. Corresponding dihedral angles in the second conformer are 37.1°, 63.7°, and 36.5°. The rings themselves exhibit minor deviations from planarity, with the nitrogen atom generally having the largest deviation [range 0.015(4)-0.038(4)Å and average 0.029Å]. The sideview of **150** (Conformer 1; illustrated in Figure 20) shows an *anti*-conformation. Two bridging *H*C-C*H* lie in the opposite direction on a plane such as two tricyclopyridyl rings pointing toward the other direction.

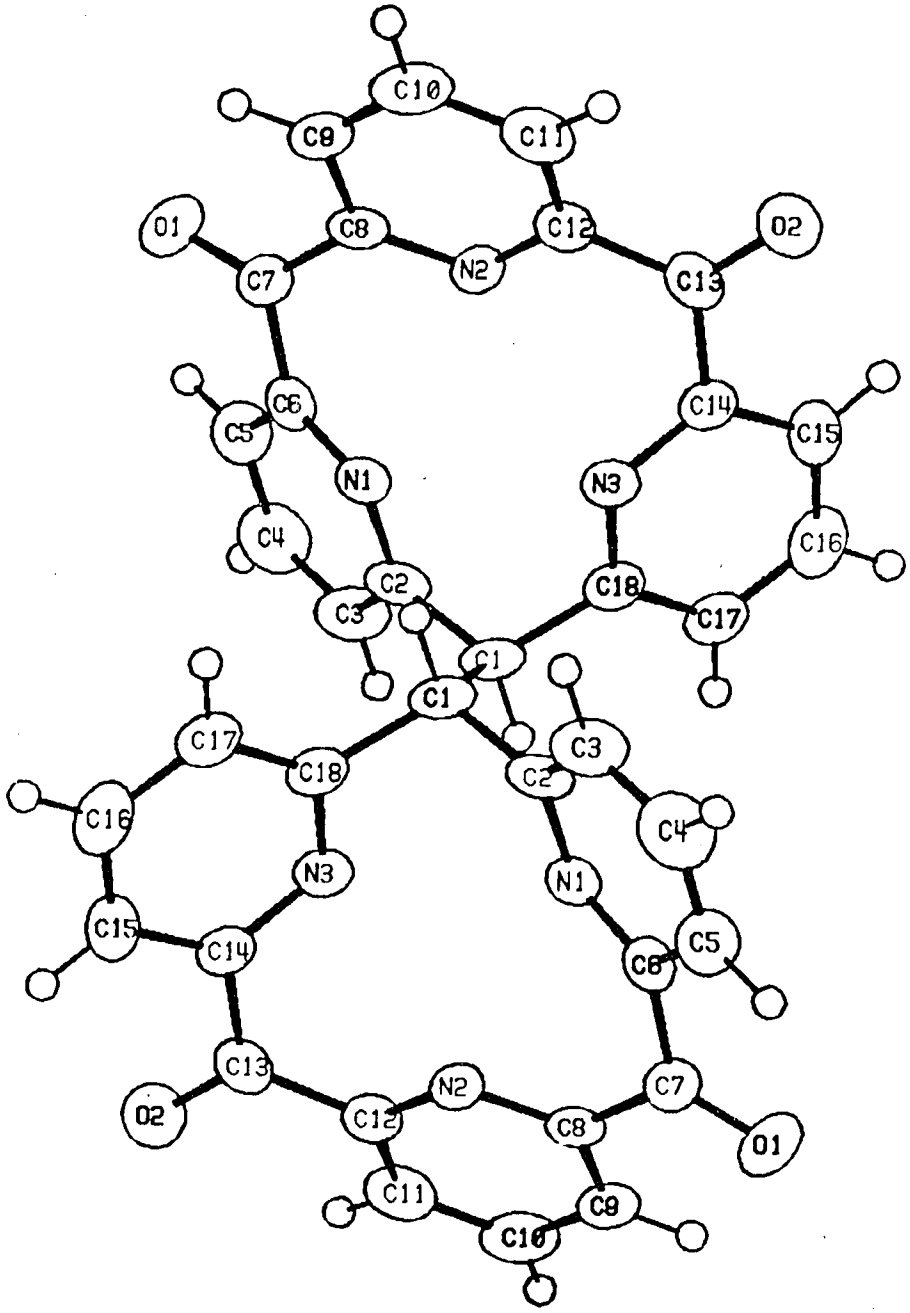


Figure 18. ORTEP of 150 (Conformer 1)

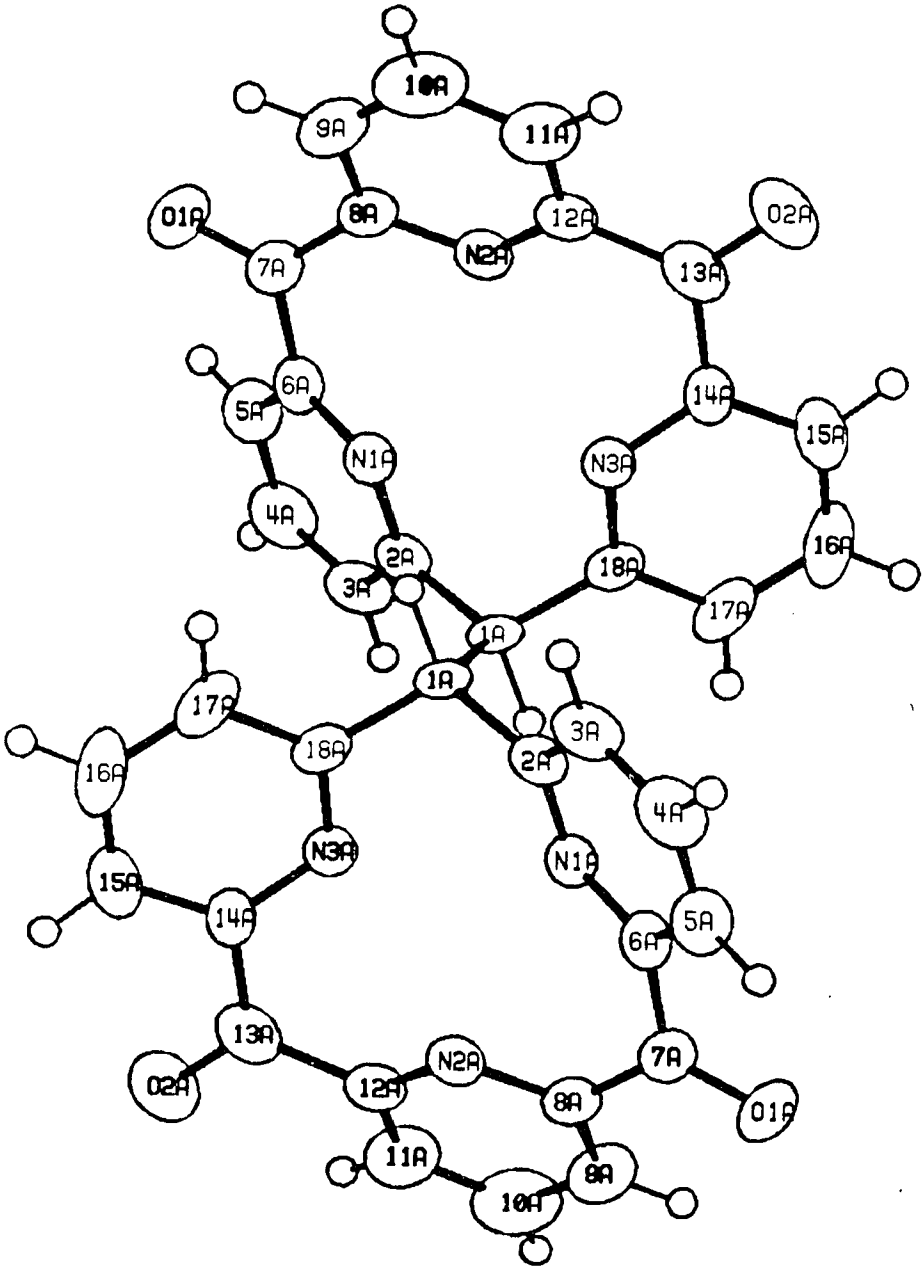


Figure 19. ORTEP of **150** (Conformer 2)

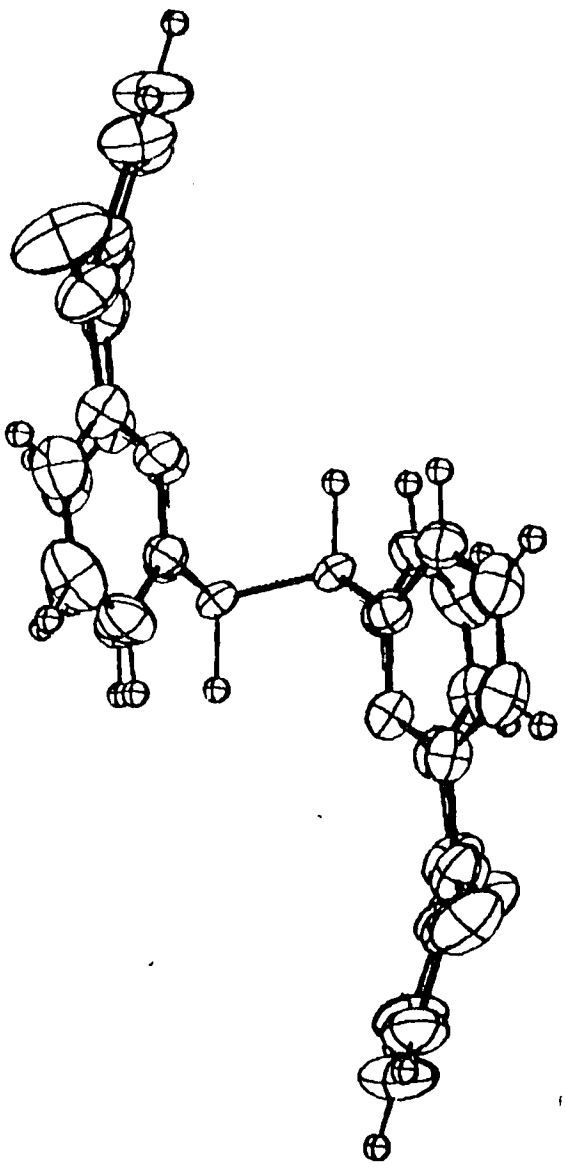
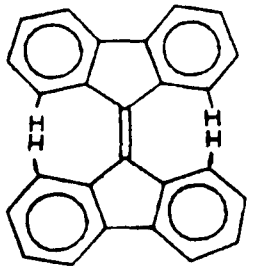
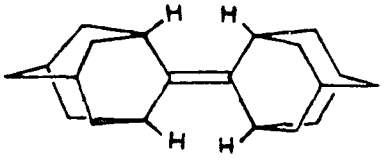


Figure 20. Sideview of **150** (Conformer 1)

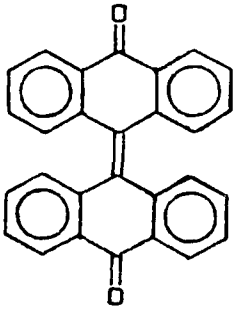
Inspection of a CPK molecular model of ethylene-bridged **151**, derived by hydrogenation of **150**, indicated that **151** should be coplanar or nearly so and belong to the family of the highly strained overcrowded ethylenes[150] which have attracted chemists' attention over the last forty years. The introduction of dynamic NMR spectroscopy as well as other modern techniques[150e-n] has enabled the spatial structure of this intriguing class of compounds to be investigated in detail in both solution and solid state. In most cases, twisted alkenes are produced if sterically demanding substituents are fixed on the same terminus of ethylene. For examples, if bifluorenylidene (**173**) were coplanar, severe nonbonding H_a-H_a repulsions would result. These destabilizing interactions may be relieved by folding or twisting at the olefinic termini.[150h] However, diadamentylidene (**174**) maintained an *untwisted* double bond in spite of the presence of significant nonbonding hydrogen repulsions.[150f]



173



174



175

Dehydrogenation of **150** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene afforded (87%) olefin **151**, which was recrystallized from $CHCl_3$, as *colorless* needles. Dimer **150** could

also be converted quantitatively to **151** with aeration in $CHCl_3$ for several days. The ^1H NMR spectrum of **151** appeared to be a combination of trione **115** and **150** (Fig. 17). The 3-, 4-, and 5-py*H* showed the same pattern as **150**, except for the greater downfield shift due to the more highly strained connecting bond. The downfield shifts of 3- and 5-pyridyl hydrogens were more dramatic than that of the 4-py*H*. However, 3′- and 4′-py*H* exhibited the similar pattern to trione **115** including their relative downfield shifts. The MS data were dominated by the parent peak at *m/e* 598.

The structure of **151** is illustrated in Figure 21. The molecule lies on a center of symmetry and has approximate symmetry C_{2h}. The disposition of the pyridyl rings is analogous to that seen in **150**. Dihedral angles between the planes of pyridine rings are N1/N2 32.6°, N1/N3 61.9°, and N2/N3 32.5°. Deviations of nitrogen atoms from these best planes are N1 0.025(4), N2 0.018(4), N3 0.025(4)Å. The central olefinic bond has a bond length of 1.360(7)Å; the corresponding bond length in **173** was not significantly different (1.38 and 1.35Å for A and B form, respectively).[151b] Indeed, an early X-ray crystallographic investigation[151a] of the crystal and molecular structure of bianthrone (**175**) indicated that the molecule adopts in the ground state a folded centrosymmetric geometry; the central rings are boat shaped and a tricyclic halves are folded in opposite directions at the ethylenic group of bond length 1.31Å. The structure of **151** thus resembles previously analyzed **115** as well as **173** and **175** in which the distortions within the molecule are not localized but are

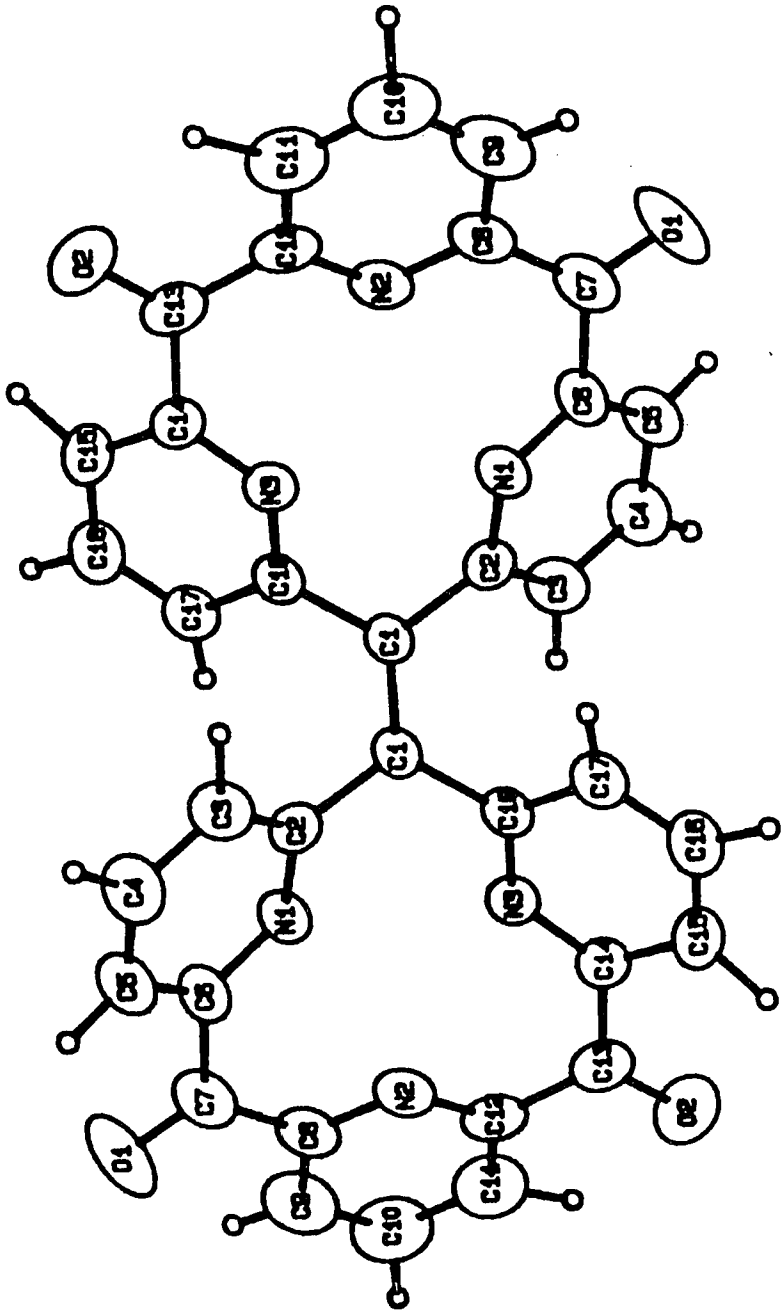


Figure 21. ORTEP of 151

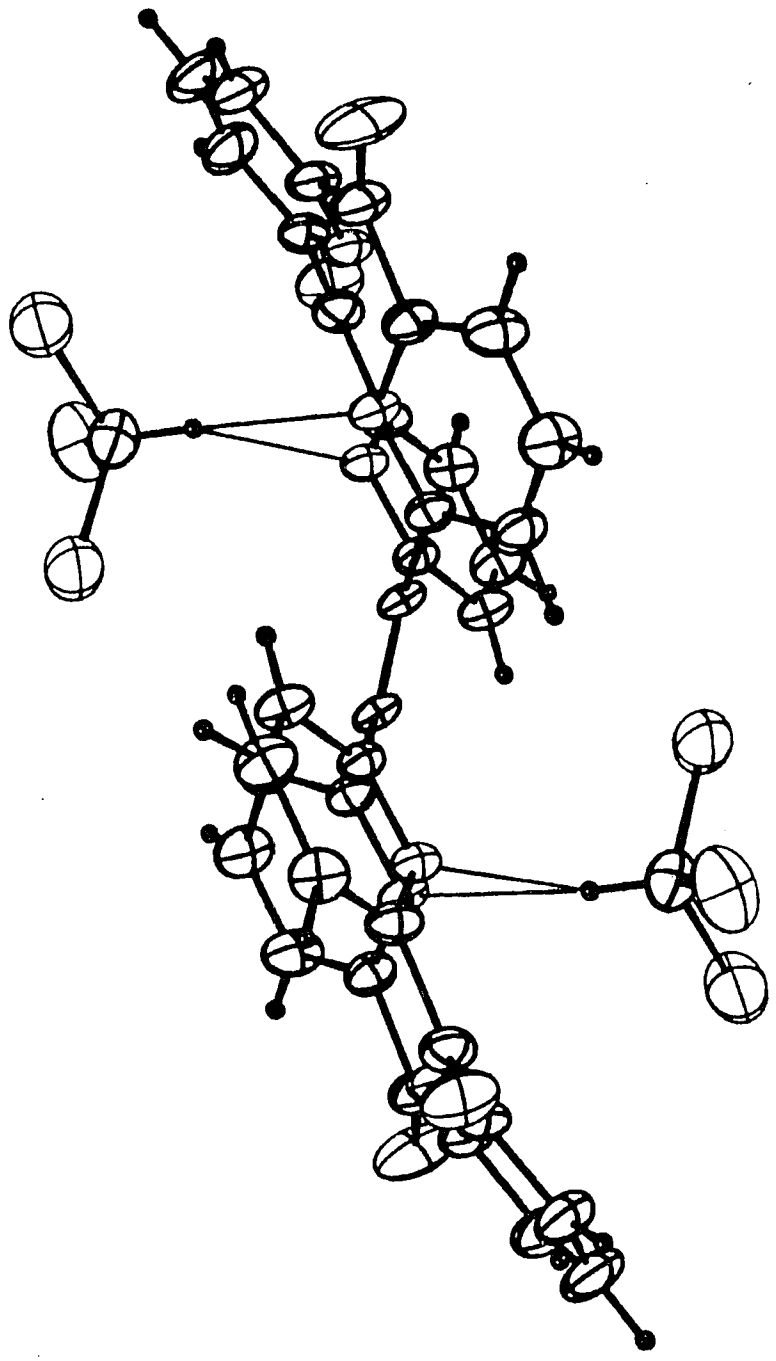


Figure 22. Sideview of **151** including two of the four $CHCl_3$ molecules

distributed over several bonds. Two of the four chloroform molecules are loosely associated with the tripyridyl moieties, as illustrated in Figure 22. The hydrogen atoms of chloroforms lie approximately 2.45Å from N3 and 2.52Å from N1.

Ethylene-bridged **151** contains again only sp^2 carbons and should be essentially planar. However, the observed deformation from planarity must be predominately due to *N-N*-lone pair repulsion within confines of the two cavities like trione **115**. Both **150** and **151** possess two unusually crowded 6*N*-electron-rich cavities and could be oxidized with SeO_2 in glacial acetic acid to afford (80%) trione **115**. Usually *C-C* bonds are inert toward SeO_2 oxidation. However, in this experiment trione **115** formation indicated that the bridged sp^3 (**150**) or sp^2 (**151**) carbon orbital flanked by cyclic pyridine units is highly activated toward [SeO_2] oxidation. In order to prove that this kind of oxidation is not usual in pyridine chemistry some other model compounds with pyridine methylene linkage would be neccessary; further studies were not conducted.

VII-6. Synthesis of Tetraketone 125

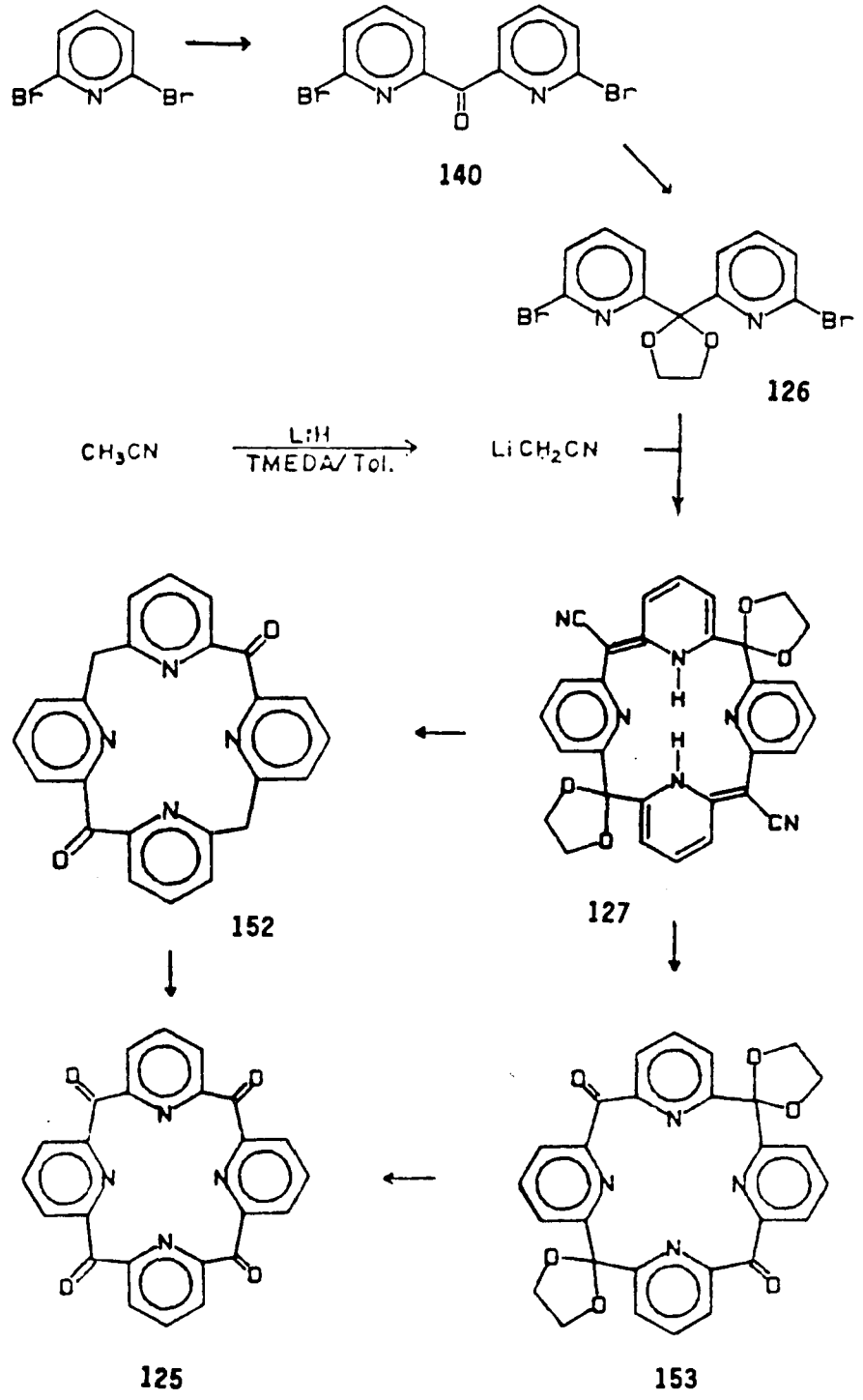
Trione **115** should be an ideal structure to probe the electronic and/or steric effects of *N*-lone pairs within a highly rigid cavity. Three pyridine rings of **115** form dihedral angles of 35.4°, 41.4°, and 46.5° with each other: this observed deformation from planarity must be predominately due to *N-N*-lone pair repulsion within the confines of the cavity (CHAP VII-3). Tetraketone **125**,

the next higher homolog, possesses a 16-membered inner core analog to the tetrapyrrolic derivatives called "xanthophorphyrinogen" (Chap. III-3). Tetraketone **125** should be the first compound in a series of a new pyridine-containing xanthoporphyrinogens as well as be the first entrant into the new area of *heterocalixarenes*.

The synthetic route, similar to that used to prepare trione **115**, was used to form **125**. (Scheme 8) Monoketone **140** was synthesized (63%) by treatment of 2-lithio-6-bromopyridine (**141**) with ethyl chloroformate at <-60°C in Et_2O. Ketalization of **140** conducted under either standard acidic[131] or basic[119,121c] conditions gave (90%) 2,2-*bis*-2'-(6'-bromopyridyl)-1,3-dioxolane (**126**). Lithioacetonitrile reacted with monoketal **126** to produce (22%) an orange crystalline macrocycle **127**. The macrocyclization efficiency is another example of the ability of the *N*-binding sites to wrap in an appropriate "metal template" to ensure the proper position of the termini for ring-closure.

The ^1H NMR spectrum of **127** showed a singlet at δ15.0 for two N-*H* protons, which were not readily exchanged in D_2O at 25°C. Pyridyl hydrogens showed a complicated pattern at δ6.84-7.53 indicative of a *non-planar* cyclic structure. A complicated pattern at δ4.14-4.34 for the ketal hydrogens was due to their unique environments, since the molecule lacked any mirror planes. Supportive ^{13}C NMR data of **127** exhibited only ten signals, of which the methine carbons appeared at δ70.4 and ketal carbons were at δ65.0 and 66.6 due to non-equivalence caused by molecular asymmetry. The pyridine carbons were observed at the expected

Scheme 8


Br
N
Br
O
140
126
CH3CN
LiH
TMEDA/Tol.
LiCH2CN
NC
CN
H
127
152
153
125

normal positions and the O-*C*-O appeared at δ110.0. The MS data were dominated by the parent peak at m/e 530. Other characteristic features of **127** were an usually high melting point [390°C (dec)] and a telltale spike at 2190cm^{-1} in IR spectrum for the conjugated nitrile.

Figure 23 illustrates the crystal structure of **127**, which exists in the tautomeric form; C12 and C24 are planar and two pyridines are protonated. Half of hydrogens were observed as N1*H* and N3*H* bonds, the other half formed N4*H* and N2*H* bonds with the same bond lengths, due either to a statistical distribution of N*H* tautomers in the crystal or to rapid interconversion of the tautomers on the NMR time scale.[72] This tautomeric form rendered each conjugated dipyridyl-methine unit nearly planar: this 15 atom-unit containing N1, N4, and N5 is *planar to within 0.18*Å, and the atoms of corresponding unit containing N2, N3, and N6 lie within 0.08Å of a common plane. These planes intersect at an angle of 94.7°. Examination of CPK models indicated that the *syn*-orientation of the two ketal rings allowed conjugation of the dipyridylmethine units, while the *anti*-orientation would prohibit it.

Macrocycle **127** was deprotected with alcoholic HCl to give (≥80%) dione **152**, which was very insoluble in most common organic solvents (e.g. $CHCl_3$, EtOH, DMSO, DMF, and *n*-hexane). The ^{1}H NMR of **152** showed a doublet at δ4.09 (J=3.8Hz) for methylene bridge hydrogens and the pyridine hydrogens appeared as a complicated pattern in the usual heteroaromatic region. The MS data were

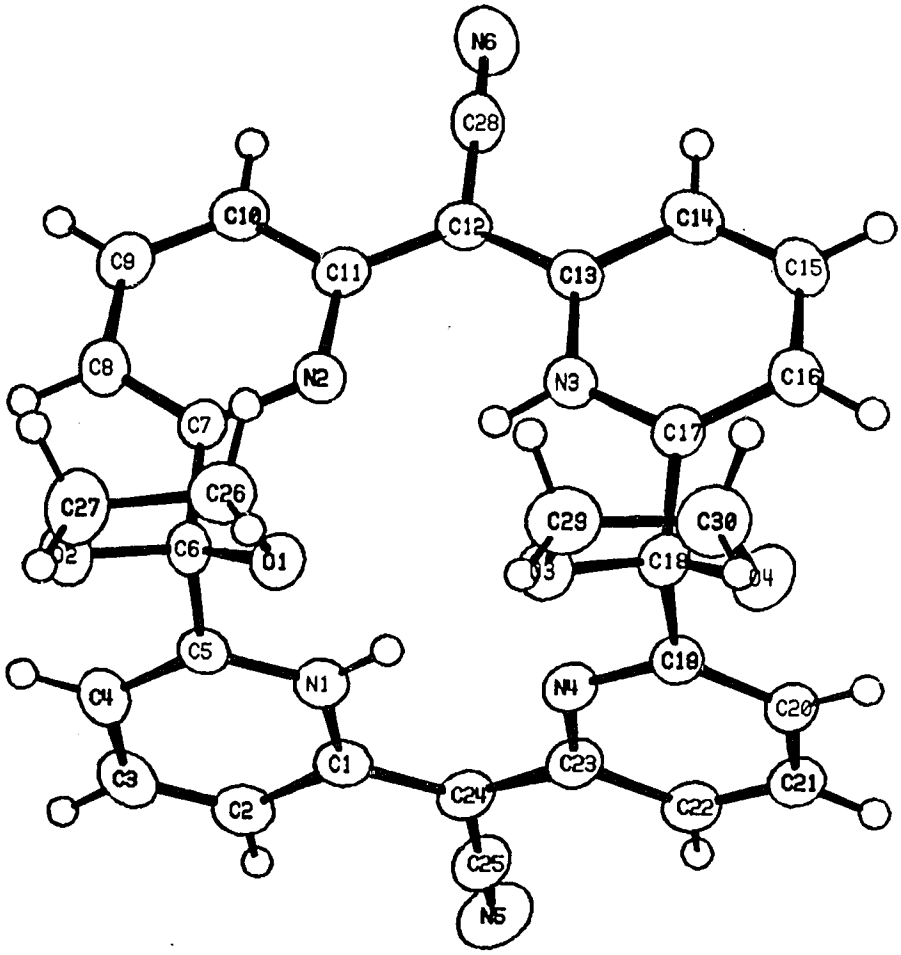


Figure 23. ORTEP of 127

dominated by the parent peaks at m/e 393 (M^++1, 33) and 392 (M^+, 93).

Without further purification, crude **152** was oxidized with SeO_2 to afford a dark grey oil, which was chromatographed (silica gel, 10% HOAc/EtOH) to give (80% from **127**) the desired tetraketone **125**, as colorless needles.

The symmetric structure of **125** was initially confirmed by its ^{13}C NMR spectrum; δ125.7 (*C*3), 137.8 (*C*4), 155.1 (*C*2), and 195.0 (*C*=O). Surprisingly, the ^1H NMR (80MHz) showed a broad singlet at δ7.91 for the 3- and 4-py*H*, whereas at higher field (400MHz), a sharp multiplet at δ7.89-7.94 was observed. The MS data exhibited principle peaks at m/e 421 (M^++1, 29) and 420 (M^+, 100). A hypsochromic shift[152] was observed for the *K*-band in the UV spectrum of **125** compared to that of trione **115**; 220nm (log ε=4.69) for **125** and 227nm (log ε=4.43) for **115** in CH_3CN. This effect indicated that the π-orbitals of four carbonyl groups deviated more from coplanarity of pyridine rings than those of trione **115**. This interpretation was corroborated by the bathochromic shift of B-band which appeared at 275nm (log ε=4.39) in CH_3CN; 250nm (log ε=4.36) for trione **115**. These spectral data supported a structure with a high degree of molecular symmetry with non-planarity. The high melting point [380°C (dec)] and again low solubility in common organic solvents were indicative of the symmetric nature of **125**, similar to known calixarenes.[24,45,52,54,55]

Figure 24 illustrates the molecular structure of **125** in which **125** is severely distorted from a planar conformation into a saddle

shape, with *N*-lone pairs pointing alternately above and below the best plane of the four nitrogen atoms. The nitrogen atoms form an approximate square, with N··N distances ranging from 3.012(4)-3.388(4)Å, angles ranging 86.7(3)-93.5(3)°, and maximum deviation from the best plane 0.113(2)Å. The closest distance across the diagonal of this approximate square is 4.406(4)Å. The eight N-C-C-C torsion angles in the 16-membered heterocycle range from -93.6(2)° to 47.2(2)°. The N-C bond distances average 1.342Å, C=O distance 1.211Å, aromatic C-C 1.379Å, and nonaromatic C-C 1.500Å. Tetraketone **125** contains only sp^2 atoms, like trione **115**, but exhibits a greater deviation from planarity than **115**. This distortion from a planar conformation into a saddle shape must be predominately due to *N*-*N*-lone pair repulsion within confines of the cavity.

Alternatively, **125** was prepared by the oxidation of **127** with *m*-chloroperbenzoic acid[144] to give diketal **153**, which could be deprotected with concentrated HCl to afford tetraketone **125**. Oxidation of **127** with *m*-chloroperbenzoic acid afforded the very insoluble diketal **153** *via* an epoxidation[120] of the exocyclic double bonds. The ^{1}H NMR spectrum of **153** showed a singlet at δ4.06 for the two ketal methylenes as well as a complicated pattern at δ7.40-7.71 due to configurational rigidity. The MS data were dominated by the parent peak at m/e 508. Without further purification, crude **153** was deketalized with concentrated HCl to afford (70% from **127**) tetraketone **125**.

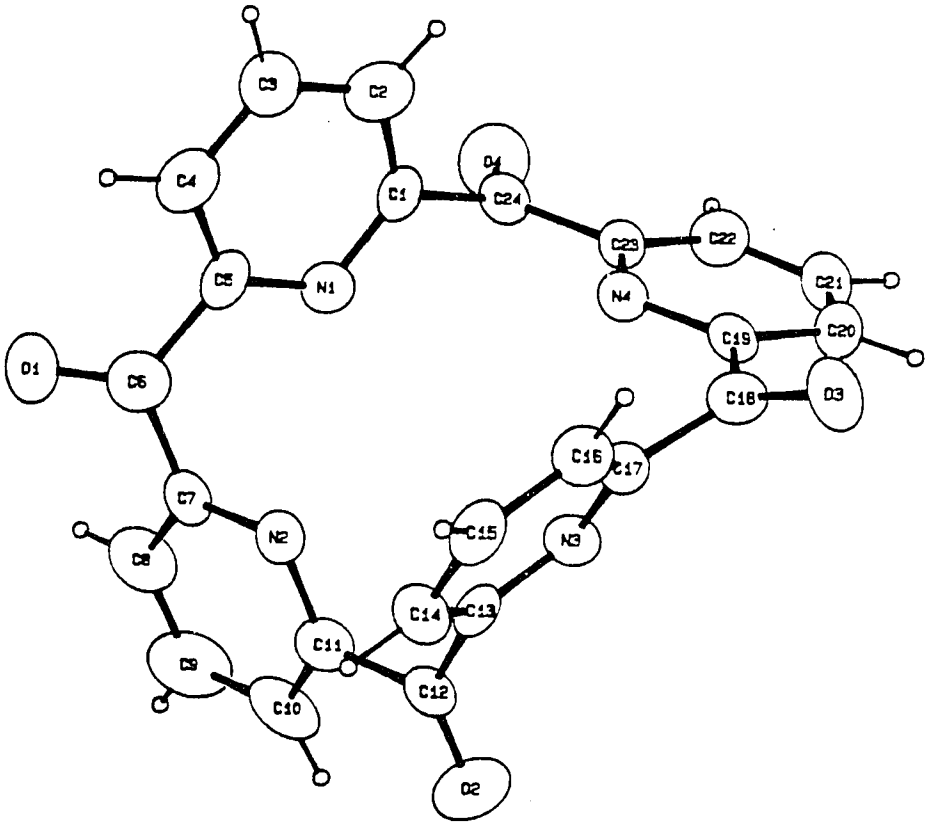
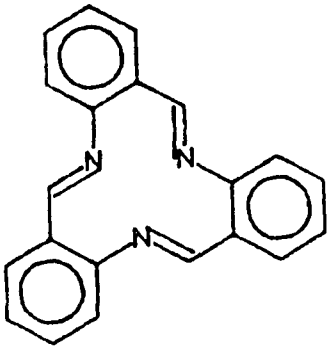


Figure 24. ORTEP of 125

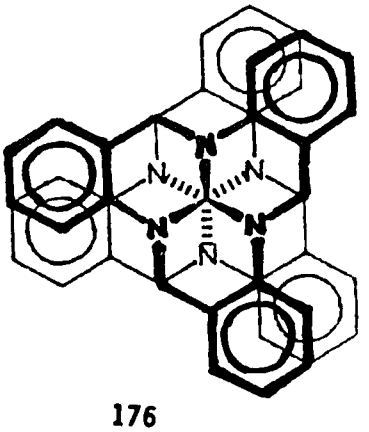
In the hopes of generating metal complexes, tetraketone **125** was treated with $FeCl_3$, $CoCl_2$, or $CuCl_2$ in warm EtOH/$CHCl_3$ (or CH_3CN), but uncomplexed **125** was recovered in vain. Other modifications, for examples, reduction with BH_3 and *N*-oxide formation with *m*-chloroperbenzoic acid, were not successful. Extremely low solubility in common organic solvents was the major obstacle to modification reactions of **125**; ca. 100mg in 50mL of $CHCl_3$, ca. 1mg in 100mL of CH_3CN, and less than 1mg in 100mL of CH_3OH, THF, ethyl ether, and benzene.

VII-7. Transition Metal Complexation of Trione 115

It is known[117] that *o*-aminobenzaldehyde underwent self-condensation in the presence of transition metal ions to form a complex containing the closed, tridentate macrocycle tribenzo-[b,f,j][1,5,9]triazacycloduodecine (**117**). Based on the spectroscopic data, sandwich complex **176** was proposed to be *N*-chelated with the six imine moieties.



117



176

From models and the results of the X-ray crystal study,[117] it is evident that the local symmetry of **176** is D_3 and that the CD spectrum[117c] should be correctly interpreted using this point group.

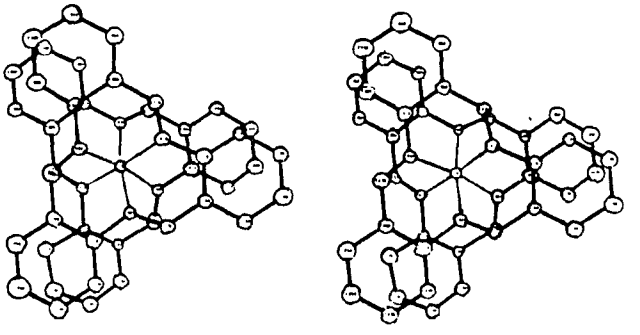
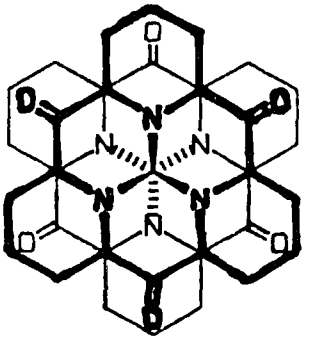


Figure 25. Stereopair[117d] of **176**

Inspection of a CPK molecular model of trione **115** indicated that it should similarly generate a transition metal ion "sandwich" complex, e.g. **177**, in which the high electron density in the vicinity of the cavity should enhance its chelating abilities.



177

Treatment of **115** with $FeCl_3$ in warm $EtOH/CHCl_3$ afforded an orange solution, from which yellowish orange crystals were obtained

by slow evaporation of the solvents. The crystals were clear and well-formed at first inspection; unfortunately, all crystals tested proved to be twinned and, therefore, unsuitable for X-ray analysis.

Treatment of 115 with $CuCl_2$ in $EtOH/CHCl_3$ gave a pale green solution, from which a white powder immediately precipitated. For good measure, this white solid was refluxed gently overnight under an inert atmosphere. These white microcrystals were moderately soluble in mixed solvents ($CHCl_3$:EtOH=9:1, v/v), but crystals grown from such a solution quickly clouded, probably as a result of solvent loss. Slow evaporation of $EtOH/CHCl_3$, however, afforded large, dark green crystals (178) suitable for an X-ray structure determination.

Complex 178 consists of a neutral hemiethylketal, not the triketone 115, in which Cu(II) is incorporated with a Jahn-Teller distorted, octahedral coordination. The Cu(II) core exhibits an octahedral array of the three nitrogens, two chlorides, and one hemiethyl ketal oxygen (See: Figure 26 and 27). The hemiethyl ketal backbone, which arose from the strained trione 115 during

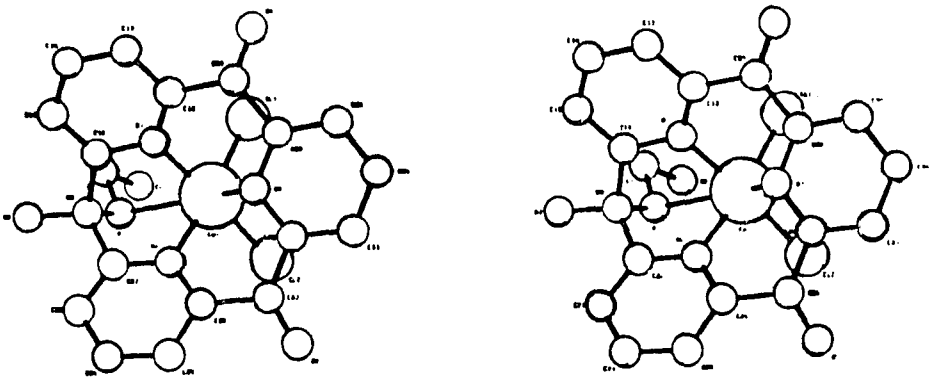


Figure 26. ORTEP Stereoview of 178

recrystallization from EtOH/$CHCl_3$, is severely distorted from a planar conformation. The planar pyridine rings make dihedral angles 64.5° (N1-N2), 33.0° (N1-N3), and 35.5° (N2-N3). Three nitrogens of the pyridine rings facially coordinate; the bond lengths of Cu-N1 and Cu-N2 are 2.033(9) and 2.022(8)Å, respectively; however, Cu-N3 bond length is 2.362(10)Å. Distortion of the octahedral geometry by axial elongation results in *Cu*-hemiketal O1 distance of 2.468(8)Å indicative of the relative weak interaction. Axial elongation also permits chelation to the metal to occur with a "bite" angle of 83.6(4)° for N1-Cu-N2, 76.3(4)° for N1-Cu-N3, and 77.2(4)° for N2-Cu-N3; Cu-N bonds are tilted slightly away from the pyridine rings. The Cl1-Cu-Cl2 angle is 95.5(2)° and an average bond length Cu-Cl is 2.241Å: these values are strikingly similar to those of Cu(II) complex of 2,2-*bis*(2′-pyridyl)-1,3-dioxolane (157);[131b] 95.71(2)° for Cl-Cu-Cl angle and 2.271Å for an average bond length for Cu-Cl.

The similar stability of the "hemiketal" complexes was reported by Osborne and McWhinnie[153] during the preparation of complexes of *bis*(2-pyridyl)ketone (145), exclusively with Cu(II) salts. The 1:2 (metal:ligand) ionic perchlorate precipitated as a dihydrate [ν(C=O)=1448cm^{-1}] and the 1:1 halides crystallized from EtOH with one mole of solvent [X=Cl, ν(C=O)=1445cm^{-1}; X=Br, ν(C=O) =1446cm^{-1}]. The water or alcohol was expelled from the adducts upon heating, to give complexes that displayed carbonyl bands shifted to much higher frequencies (1693-1707cm^{-1}). The physical change was attributed to an alteration in the mode of complexation

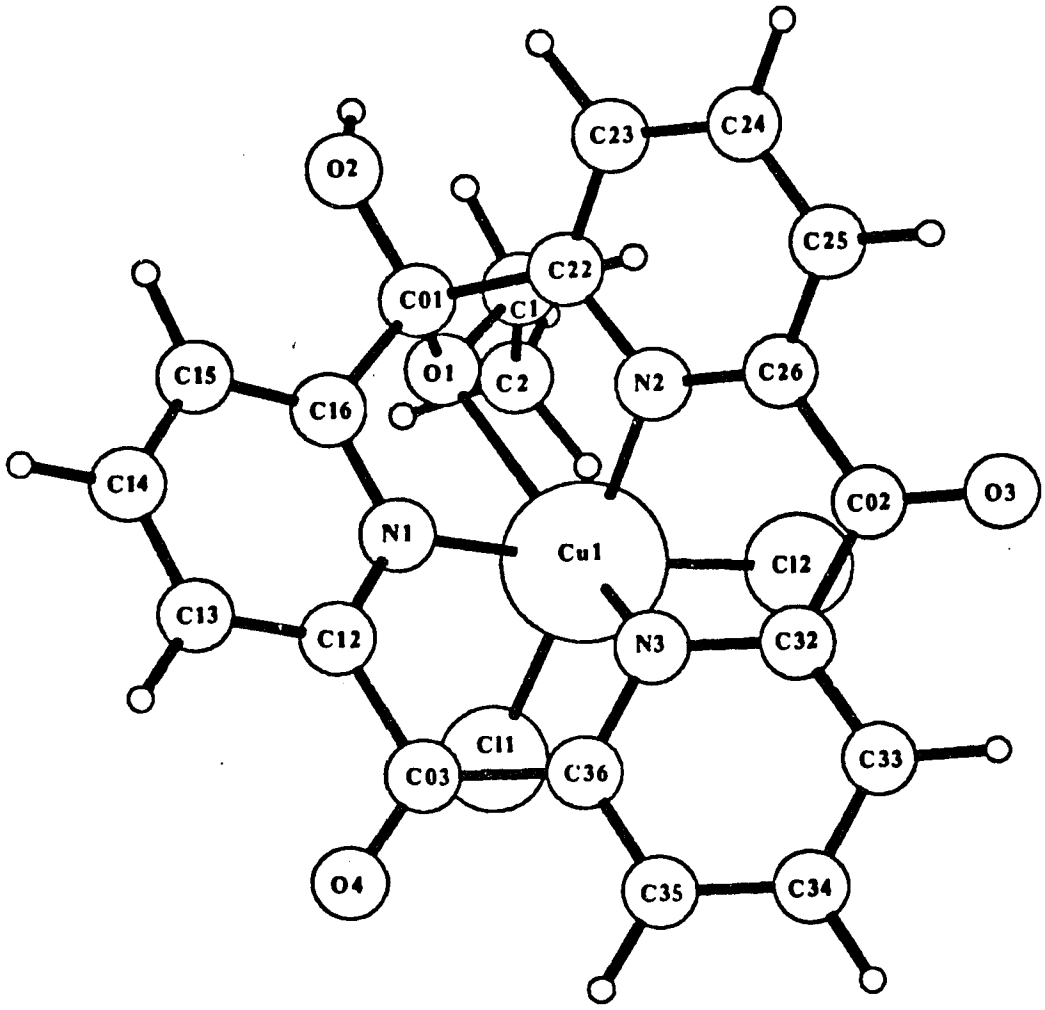
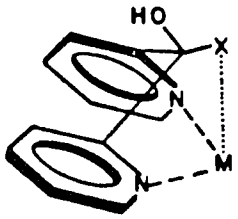


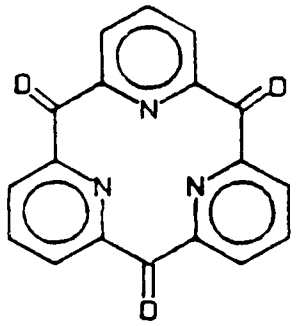
Figure 27. ORTEP of 178

from *N,O* to *N,N*; water (or solvent) molecules had added across the ketone of N,N-coordinated **145** to yield stable *gem*-diols. Further studies[154] demonstrated that addition to nucleophilic HX occurred after the formation of the *N,N*-coordinated complex, and that the serendipitous disposition of X provided the possibility of tridentate chelation by carbonyl adducts of **145**.

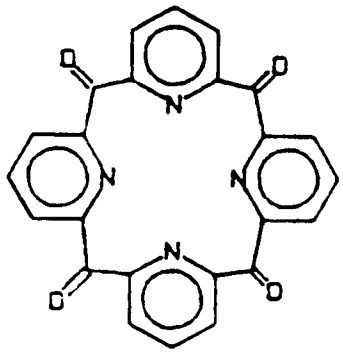


CONCLUSION

Fundamental understanding of the structural, electronic, and chemical properties of naturally-occurring and related artificial macrocycles as well as complexes has been one of the long-range goals of this research project. In order to understand, and to be able to reproduce, the ion or molecular specificity of naturally occurring chelating agents, the synthesis of models **115** and **125** has been undertaken.



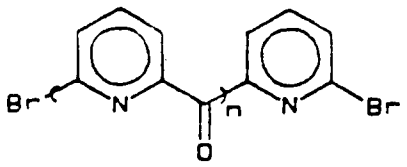
115



125

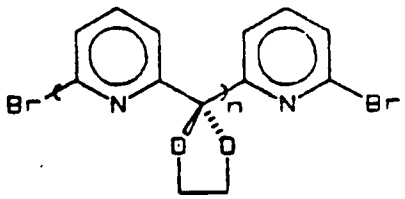
Preparation of macrocycles **115** and **125** demanded the ability to synthesize the 2-pyridyl ketone unit: *bis*-2-(6-bromopyridyl)ketone (**140**) and 2,6-*bis*[2′-(6′-bromopicolinoyl)]pyridine (**142**). 2-Bromo-6-lithiopyridine, generated from 2,6-dibromopyridine and *n*-butyllithium, was used to synthesize these ketones. Both acid- and base-catalyzed ketalizations were employed, the former was far preferable.

When the attempt was made to cyclize the resulting ketals, a new nucleophilic substitution route was discovered. Lithioaceto-



140 (n=1)

142 (n=2)



126 (n=1)

123 (n=2)

nitriles were allowed to react with bromopyridines to produce symmetrical and unsymmetrical cyanomethine adducts in more than 47% yield. In general, the symmetrical cyanomethines were prepared (<20%) from 2-(or 4-)halopyridines (or quinolines) with $NaNH_2$ and CH_3CN, and the synthesis of the unsymmetrical cyanomethines was not reported. The characteristic spectral features of these cyanomethines are the conjugated nitrile absorption (IR) in the range of 2160-2200 cm^{-1}, a broad singlet (^1H NMR) at $\delta 15.7 \pm 0.8$ ($CDCl_3$) for the N-H N bond, and the signals (^{13}C NMR) in the region of $\delta 70+6$ for the methine-bridge sp^2-carbon atoms. Other physical features are typically high melting points, compared to structural counterparts, and low solubility in common organic solvents, which frequently poses purification and characterization problems. The tautomeric equilibrium in the solid state of *meso*-cyano compound **165** was ascertained by an X-ray crystal structure, in which the methine carbon is planar and only one of the pyridyl units is protonated; the N-H [bond length 0.931(12)Å] hydrogen forms a bifurcated hydrogen bond with H(N1)-N3 [1.876(12)Å] and H(N1)-O1 [2.219(11)Å]. The bond length data afford a rationale to why the

methine carbons (^{13}C NMR) appear at $\delta 70\pm6$ instead of double bond region.

Reaction of **126** or **123** with lithioacetonitrile afforded [1$_n$](2,6)pyridinophanes (n=3,4), in which the pyridine rings were coupled with ketal and cyanomethine functionalities. At 80°C, cyclocondensation *via* nucleophilic substitution favored macrocycle formation because the intermediates are held in the desired *syn*-conformation by a metal ion template effect. The tautomeric behavior of the methine bridge of **124** and **127** was ascertained by NMR as well as IR and X-ray analyses.

Hydrolysis of the ketal and nitrile groups under acidic conditions gave methylenic intermediates, which were oxidized with SeO_2 to afford the desired trione **115** and tetraketone **125**. A possible reaction pathway for the loss of the nitrile can be envisioned to proceed *via* a six-centered trasition state. Alternatively, a facile epoxidation of the α,β-unsaturated nitrile tautomers with *m*-chloroperbenzoic acid to afford cyanohydrins, which smoothly eliminated cyanide to afford a keto group; followed by deketalization under acidic conditions afforded the same ketones.

Trione **115** and tetraone **125** contain only sp^2 ring atoms and should be essentially flat - barring any direct *N*-electron interactions; however, the observed deformation from planarity must be predominantly due to *N,N*-lone pair repulsions within the confines of the cavity. The dihedral angles of pyridines in trione **115** are 35.4, 41.4, and 46.5°; the eight N-C-C-C torsion angles in

the 16-membered heterocycle of tetraone **125** range from -93.6(2)° to 47.2(2)°.

Wittig reactions and the Knoevenagel condensations on the bridging carbonyl groups in triketone **115** were unsuccessful, but facile monohemiketalization of **115** was observed. Single crystal X-ray analyses of hemiketal **167**, diketal **120**, and monoketal **119** were performed, in which deformations from planarity were observed.

X-ray analysis of a Cu(II) complex isolated from ethanol confirmed the presence of a hemiethyl ketal (**178**). The similar stability of the "hemiketal" complexes was reported by Osborne and McWhinnie[153] during the preparation of complexes of *bis*-(2-pyridyl)ketone (**145**), exclusively with Cu(II) salts.

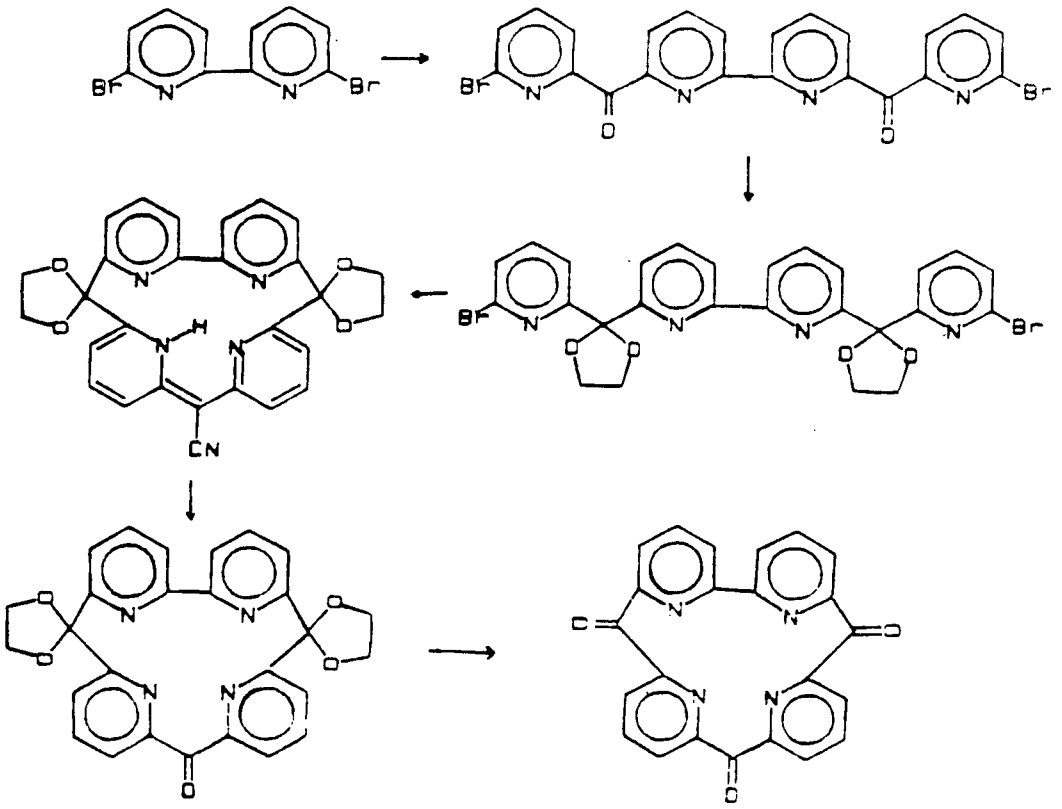
Upon exposure to air, precursor **143** of triketone **115** underwent oxidization to afford dimeric $[1_3]$(2,6)pyridinophane **150**. Each tripyridino subunits has the conformation seen in the analogous trione **115** with two *N*-lone pairs tipped out-of-the-plane on one side, and the third tipped on the opposite direction, yielding local C_s symmetry. Two bridging *HC*-C*H* lie in the opposite direction on a plane such as two tricyclopyridyl rings pointing toward the other direction. Dehydrogenation of **150** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded olefin **151**. Dimer **150** could also be converted quantitatively to **151** with aeration in $CHCl_3$ for several days. Ethylene-bridged **151** contains again only sp^2 carbons and should be essentially planar. However, the observed deformation from planarity must be predominately due again to *N*-*N*-lone pair repulsion within confines of the two

cavities like trione **115**. Both **150** and **151** possess two unusually crowded 6*N*-electron-rich cavities and could be oxidized with SeO_2 in glacial acetic acid to afford (80%) trione **115**. Usually *C-C* bonds are inert toward SeO_2 oxidation. However, in this experiment trione **115** formation indicated that the bridged sp^3 (**150**) or sp^2 (**151**) carbon orbital flanked by cyclic pyridine units is highly activated toward [SeO_2] oxidation.

Associated with the synthesis of (2,6)pyridinophanes herein performed, the synthesis of **179** (corrin model) and **180** were very interesting. CPK molecular models indicate that both pyridinophanes are highly strained frameworks, however, constructable by application of the same reaction route as shown in Scheme 9 and 10.

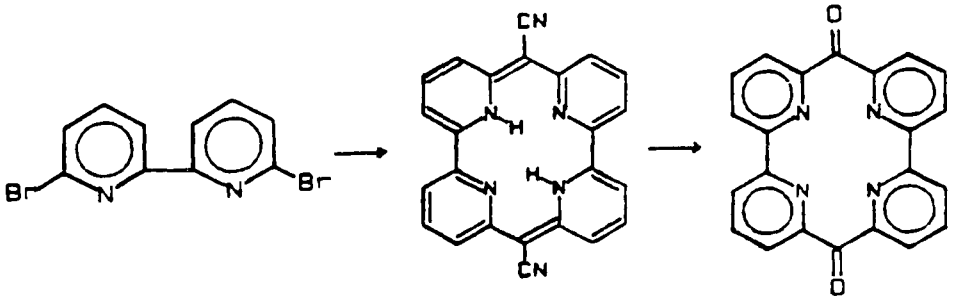
For elucidating the unique electronic and structural relationships between (2,6)pyridinophanes and known biological systems the chemistry of "pyridyl-porphyrin" skeletons will be conducted through partial reduction (chemical and electrolytic) and substitution reactions, which will permit functionalization of the periphery as well as synthesize the novel metalloheteromacrocycles. For examples, tetraone **125** possesses 16-membered inner core analogous to many imine and porphyrin systems, except **125** is at the wrong oxidation state to be oxidatively comparable to the porphyrin inner ring. Of the reduction products, **181** and **182** are by far the most important due to their direct oxidative relationship to the porphyrin skeletons. Whereas **181a** would be unstable for the vinyl alcohol bridges, **181b** would possess a pronounced structural similarity to **127**. Chemical reduction of **181b** can also be

Scheme 9. Proposed Reaction Routes for 179

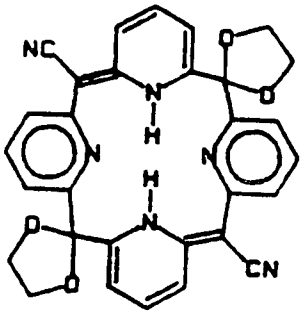


179

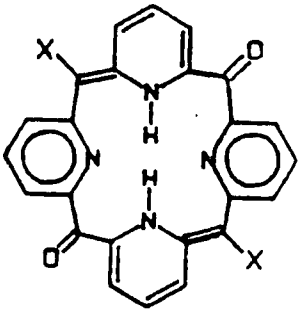
Scheme 10. Proposed Reaction Routes for 180



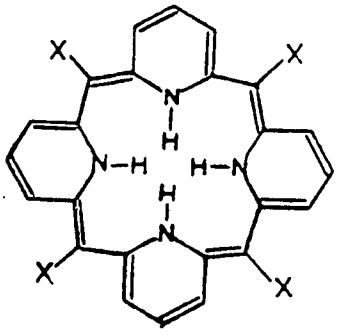
180



127



181a, X = OH
181b, X = CN



182a, X = OH
182b, X = CN

conducted to afford **182b**; the ability to control the specificity will probably be more difficult.

The future work in this field of (2,6)pyridinophanes must include the modification of the carbonyl functionality to increase the *N*-electron density within the macrocyclic core. Recently, new methods of carbonyl methylation were reported with trimethylstannylmethyllithium,[155a] CH_2I_2-Zn-$TiCl_4$,[155b] CH_2I_2-Zn-Ti-$(O\text{-}^iPr)_4$,[155c] CH_2I_2-Zn-Me_3Al,[155c] $Cl_2W(O)=CH_2$,[155d,e] and $W[=\overline{C(CH_2)_3CH_2}](OCH_2Bu)_2X_2$.[155f,g] These methods have proven to be suitable for carbonyl olefination of alkyl and phenyl group. The only limiting factor of carbonyl olefination in π-deficient pyridine chemistry is the researchers' imagination and forethought.

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APPENDIX

Table A1. Bond Distances (Å) and Angles (°) for **165**.

Bonds	Å	Angles	°
O1-C1	1.406(1)	C1-O1-C2	114.5(1)
O1-C2	1.379(1)	C15-O2-C16	113.0(1)
O2-C15	1.404(1)	C3-N1-C7	123.9(1)
O2-C16	1.407(1)	C10-N3-C14	119.3(1)
N1-C3	1.357(1)	O1-C2-C3	110.2(1)
N1-C7	1.365(1)	N1-C3-C2	116.7(1)
N2-C9	1.148(1)	N1-C3-C4	119.8(1)
N3-C10	1.350(1)	C2-C3-C4	123.5(2)
N3-C14	1.343(1)	C4-C5-C6	121.1(1)
C2-C3	1.498(2)	C5-C6-C7	120.5(1)
C3-C4	1.357(1)	N1-C7-C6	116.1(1)
C4-C5	1.400(2)	N1-C7-C8	120.1(1)
C5-C6	1.350(1)	C6-C7-C8	123.9(1)
C6-C7	1.418(1)	C7-C8-C9	116.8(1)
C7-C8	1.410(1)	C7-C8-C10	125.9(1)
C8-C9	1.417(1)	C9-C8-C10	117.2(1)
C8-C10	1.452(1)	N2-C9-C8	179.4(2)
C10-C11	1.401(1)	N3-C10-C8	118.3(1)
C11-C12	1.370(1)	N3-C10-C11	120.4(1)
C12-C13	1.385(1)	C8-C10-C11	121.3(2)
C13-C14	1.382(1)	C10-C11-C12	119.5(1)
C14-C15	1.496(1)	C11-C12-C13	120.0(1)
		C12-C13-C14	117.9(1)
		N3-C14-C13	122.8(2)
H-O1[d^3]	2.219(11)	N3-C14-C15	115.1(1)
H-N1[d^1]	0.931(12)	C13-C14-C15	122.1(1)
H-N3[d^2]	1.876(12)		

Table A2. Crystal Data and Coordinates of Nonhydrogen Atoms for **165**

$C_{16}H_{17}N_3O_2$, MW=283.3, triclinic space group P1, a=7.5310(6), b=9.9577(12), c=11.0301(12)Å, α=65.957(10), β=73.652(8), γ=85.889(8)°, Z=2, D_c=1.300gcm^{-3}, μ(MoKα)=0.82cm^{-1}, R=0.046 for 2137 observations (of 3171 unique data), 1°<θ<27°, 235 variables. All H atoms except CH_3 are refined.

Atoms	x	y	z
O1	0.1335(2)	0.2603(1)	0.5284(1)
O2	0.1155(2)	0.3208(1)	0.9411(1)
N1	0.2834(2)	0.5177(1)	0.3548(1)
N2	0.5030(3)	1.0123(2)	0.2004(2)
N3	0.2681(2)	0.5584(1)	0.5805(1)
C1	0.0748(3)	0.1169(2)	0.6275(2)
C2	0.1746(2)	0.2756(2)	0.3934(2)
C3	0.2503(2)	0.4287(2)	0.2967(1)
C4	0.2874(2)	0.4800(2)	0.1573(1)
C5	0.3594(3)	0.6248(2)	0.0767(1)
C6	0.3912(2)	0.7126(2)	0.1355(2)
C7	0.3523(2)	0.6598(2)	0.2811(1)
C8	0.3795(2)	0.7452(2)	0.3502(1)
C9	0.4482(3)	0.8925(2)	0.2669(2)
C10	0.3356(2)	0.6978(2)	0.4989(1)
C11	0.3600(2)	0.7942(2)	0.5573(1)
C12	0.3093(3)	0.7474(2)	0.6980(1)
C13	0.2354(2)	0.6055(2)	0.7816(1)
C14	0.2195(2)	0.5140(2)	0.7184(1)
C15	0.1485(2)	0.3571(2)	0.7993(1)
C16	0.0698(4)	0.1701(2)	1.0230(2)

Table A3. Important Torsion Angles (°) for **165**

C1-O1-C2-C3	-175.3
O1-C2-C3-N1	6.7
N1-C7-C8-C9	-178.8
N3-C10-C8-C9	179.3
N3-C14-C15-O2	175.7
C14-C15-O2-C16	-172.8

Table A4. Bond Distances (Å) and Angles (°) for 124

Bonds	Å	Angles	°
O1-C6	1.414(2)	C6-O1-C20	107.5(2)
O1-C20	1.425(2)	C6-O2-C21	105.3(2)
O2-C6	1.411(2)	C12-O3-C22	105.9(2)
O2-C21	1.423(2)	C12-O4-C23	108.2(2)
O3-C12	1.423(2)	C1-N1-C5	121.9(2)
O3-C22	1.425(2)	C7-N2-C11	118.1(2)
O4-C12	!.415(2)	C13-N3-C17	121.9(2)
O4-C23	1.426(2)	N1-C1-C2	118.0(2)
N1-C1	1.357(2)	N1-C1-C18	119.2(2)
N1-C5	1.357(2)	C2-C1-C18	122.9(2)
N2-C7	1.341(2)	C1-C2-C3	119.7(2)
N2-C11	1.335(2)	C2-C3-C4	121.0(2)
N3-C13	1.349(2)	C3-C4-C5	118.3(2)
N3-C17	1.360(2)	N1-C5-C4	121.2(2)
N4-C19	1.154(2)	N1-C5-C6	116.1(2)
C1-C2	1.413(2)	C4-C5-C6	122.8(2)
C1-C18	1.431(2)	O1-C6-O2	106.4(2)
C2-C3	1.354(2)	O1-C6-C5	108.9(2)
C3-C4	1.394(2)	O1-C6-C7	110.3(2)
C4-C5	1.357(2)	O2-C6-C5	108.4(2)
C5-C6	1.525(2)	C9-C10-C11	118.5(2)
C6-C7	1.528(2)	N2-C11-C10	122.8(2)
C7-C8	1.382(2)	N2-C11-C12	114.7(2)
C8-C9	1.379(2)	C10-C11-C12	122.1(2)
C9-C10	1.378(2)	O3-C12-O4	106.9(2)
C10-C11	1.378(2)	O3-C12-C11	108.8(2)
C11-C12	1.517(2)	O3-C12-C13	110.9(2)
C12-C13	1.536(2)	O4-C12-C11	110.5(2)
C13-C14	1.365(2)	O4-C12-C13	108.5(2)
C14-C15	1.397(2)	C11-C12-C13	111.1(2)
C15-C16	1.356(2)	N3-C13-C12	116.2(2)
C16-C17	1.417(2)	N3-C13-C14	121.2(2)
C17-C18	1.431(2)	C12-C13-C14	122.6(2)
C18-C19	1.421(2)	C13-C14-C15	118.4(2)
C20-C21	1.500(3)	C14-C15-C16	120.7(2)
C22-C23	1.487(3)	C15-C16-C17	119.8(2)
		N3-C17-C16	118.0(2)
		N3-C17-C18	118.9(2)
H-N1[d^1]	0.86*	C16-C17-C18	123.1(2)
H-N2[d^2]	2.16*	C1-C18-C17	125.8(2)
H-N3[d^3]	1.96*		

* the two positions H(N1) and H(N3) are unrefined and half-populated by H.

Table A5. Crystal Data and Coordinates of Nonhydrogen Atoms for **124**

$C_{23}H_{18}N_4O_4$, MW=414.4, monoclinic $P2_1/n$, a=11.104(4), b=7.544(2), c=22.375(4)Å, α=91.66(2)°, Z=4, D_c=1.469gcm^{-3}, μ(MoKα)=0.97cm^{-1}, R=0.035 for 2103 observations, 1°<θ<27°, 280 variables.

Atom	x	y	z
O1	0.3102(1)	0.2208(2)	0.07968(6)
O2	0.1726(1)	0.4393(2)	0.08961(6)
O3	-0.2441(1)	0.3001(2)	0.09840(6)
O4	-0.3114(1)	0.0153(2)	0.10419(6)
N1	0.1261(1)	0.2501(2)	0.20938(7)
N2	-0.0087(1)	0.1860(2)	0.10352(7)
N3	-0.1057(1)	0.1777(2)	0.21768(6)
N4	0.0536(2)	0.2202(3)	0.41793(8)
C1	0.1346(2)	0.2456(3)	0.26998(9)
C2	0.2503(2)	0.2622(3)	0.29746(10)
C3	0.3480(2)	0.2810(4)	0.26319(10)
C4	0.3367(2)	0.2820(4)	0.20099(10)
C5	0.2249(2)	0.2659(3)	0.17548(9)
C6	0.2020(2)	0.2653(3)	0.10796(9)
C7	0.1028(2)	0.1330(3)	0.09059(8)
C8	0.1273(2)	-0.0354(3)	0.06984(9)
C9	0.0335(2)	-0.1548(3)	0.06452(10)
C10	-0.0803(2)	-0.1045(3)	0.08066(9)
C11	-0.0977(2)	0.0674(3)	0.09933(8)
C12	-0.2171(2)	0.1303(3)	0.12301(8)
C13	-0.2131(2)	0.1371(3)	0.19166(9)

Table A5. (Cont'd)

Atom	x	y	z
C14	-0.3117(2)	0.1033(3)	0.22489(9)
C15	-0.2992(2)	0.1126(3)	0.28711(9)
C16	-0.1913(2)	0.1526(3)	0.31378(9)
C17	-0.0899(2)	0.1846(3)	0.27833(8)
C18	0.0276(2)	0.2211(3)	0.30318(8)
C19	0.0420(2)	0.2205(3)	0.36651(9)
C20	0.3176(2)	0.3286(3)	0.02762(9)
C21	0.2123(2)	0.4528(3)	0.02987(9)
C22	-0.3706(2)	0.3008(3)	0.08525(10)
C23	-0.3948(2)	0.1142(3)	0.06736(10)

Table A6. Bond Distances (Å) and Angles (°) for **167**

N(1)				
	C(1)		1.3356	0.0042
	C(5)		1.3294	0.0040
	C(1)	C(5)	118.803	0.277
C(1)				
	N(1)		1.3356	0.0042
	C(2)		1.3784	0.0054
	C(19)		1.4993	0.0046
	N(1)	C(2)	122.260	0.293
	N(1)	C(19)	116.304	0.293
	C(2)	C(19)	121.421	0.317
C(2)				
	C(1)		1.3784	0.0054
	H(2)		0.8957	0.0367
	C(3)		1.3608	0.0059
	C(1)	H(2)	116.755	2.213
	C(1)	C(3)	118.625	0.372
	H(2)	C(3)	124.517	2.180
C(3)				
	C(2)		1.3608	0.0059
	H(3)		0.9379	0.0441
	C(4)		1.3801	0.0059
	C(2)	H(3)	120.673	2.519
	C(2)	C(4)	119.862	0.397
	H(3)	C(4)	119.253	2.587
C(4)				
	C(3)		1.3801	0.0059
	H(4)		1.0418	0.0361
	C(5)		1.3860	0.0052
	C(3)	H(4)	121.803	1.899
	C(3)	C(5)	118.166	0.360
	H(4)	C(5)	119.993	1.901
C(5)				
	N(1)		1.3294	0.0040
	C(4)		1.3860	0.0052
	C(6)		1.5292	0.0047
	N(1)	C(4)	122.038	0.310
	N(1)	C(6)	114.945	0.267
	C(4)	C(6)	122.852	0.297

Table A6. (Cont'd)

C(6)				
	C(5)		1.5292	0.0047
	O(1)		1.4008	0.0037
	O(2)		1.4171	0.0046
	C(8)		1.5396	0.0048
	C(5)	C(8)	107.736	0.250
	C(5)	O(1)	106.706	0.269
	C(5)	O(2)	113.294	0.300
	O(1)	C(8)	112.181	0.308
	O(1)	O(2)	111.588	0.258
	O(2)	C(8)	105.378	0.250
O(1)				
	C(6)		1.4008	0.0037
	H(1)		0.7738	0.0517
	C(6)	H(1)	106.746	3.879
O(2)				
	C(6)		1.4171	0.0046
	C(7)		1.4319	0.0051
	C(6)	C(7)	115.533	0.290
C(7)				
	O(2)		1.4319	0.0051
	H(7A)		1.1176	0.0542
	H(7B)		1.0624	0.0616
	H(7C)		1.0477	0.0526
	O(2)	H(7A)	108.187	3.184
	O(2)	H(7B)	114.802	2.840
	O(2)	H(7C)	106.141	2.579
	H(7A)	H(7B)	106.337	3.900
	H(7A)	H(7C)	111.313	3.680
	H(7B)	H(7C)	110.120	4.320
C(8)				
	C(6)		1.5396	0.0048
	C(9)		1.3800	0.0069
	N(2)		1.3287	0.0041
	C(6)	C(9)	122.513	0.294
	C(6)	N(2)	115.074	0.325
	C(9)	N(2)	122.303	0.319
C(9)				
	C(8)		1.3800	0.0069
	H(9)		0.9612	0.0402
	C(10)		1.3740	0.0067
	C(8)	H(9)	122.096	2.628
	C(8)	C(10)	118.719	0.410
	H(9)	C(10)	119.185	2.650

Table A6. (Cont'd)

C(10)				
	C(9)		1.3740	0.0067
	H(10)		0.9445	0.0443
	C(11)		1.3809	0.0073
	C(9)	H(10)	116.021	1.980
	C(9)	C(11)	119.631	0.549
	H(10)	C(11)	124.327	1.986
C(11)				
	C(10)		1.3809	0.0073
	H(11)		0.8917	0.0395
	C(12)		1.3726	0.0075
	C(10)	H(11)	125.025	2.956
	C(10)	C(12)	118.017	0.434
	H(11)	C(12)	116.904	2.912
C(12)				
	C(11)		1.3726	0.0075
	N(2)		1.3457	0.0042
	C(13)		1.5085	0.0051
	C(11)	N(2)	122.774	0.337
	C(11)	C(13)	122.282	0.329
	N(2)	C(13)	114.930	0.348
N(2)				
	C(8)		1.3287	0.0041
	C(12)		1.3457	0.0042
	C(8)	C(12)	118.322	0.335
C(13)				
	C(12)		1.5085	0.0051
	O(3)		1.2191	0.0045
	C(14)		1.4870	0.0057
	C(12)	O(3)	120.481	0.375
	C(12)	C(14)	117.795	0.284
	O(3)	C(14)	121.724	0.341
O(3)				
	C(13)		1.2191	0.0045
	H(1)		2.0836	0.0513
C(14)				
	C(13)		1.4870	0.0057
	C(15)		1.3881	0.0059
	N(3)		1.3369	0.0045
	C(13)	C(15)	122.730	0.361
	C(13)	N(3)	115.127	0.320
	C(15)	N(3)	122.089	0.370
C(15)				
	C(14)		1.3881	0.0059
	H(15)		0.9374	0.0426
	C(16)		1.3787	0.0072
	C(14)	H(15)	111.532	2.999
	C(14)	C(16)	118.919	0.423
	H(15)	C(16)	129.234	2.944

Table A6. (Cont'd)

C(16)				
	C(15)		1.3787	0.0072
	H(16)		0.9592	0.0508
	C(17)		1.3697	0.0065
	C(15)	H(16)	121.599	2.584
	C(15)	C(17)	119.338	0.445
	H(16)	C(17)	119.060	2.588
C(17)				
	C(16)		1.3697	0.0065
	H(17)		0.9585	0.0408
	C(18)		1.3851	0.0058
	C(16)	H(17)	126.816	2.363
	C(16)	C(18)	118.428	0.424
	H(17)	C(18)	114.716	2.374
C(18)				
	C(17)		1.3851	0.0058
	N(3)		1.3346	0.0049
	C(19)		1.4997	0.0050
	C(17)	N(3)	123.039	0.333
	C(17)	C(19)	121.404	0.365
	N(3)	C(19)	115.470	0.323
N(3)				
	C(14)		1.3369	0.0045
	C(18)		1.3346	0.0049
	C(14)	C(18)	118.171	0.311
C(19)				
	C(1)		1.4993	0.0046
	C(18)		1.4997	0.0050
	O(4)		1.2140	0.0047
	C(1)	C(18)	118.053	0.307
	C(1)	O(4)	120.831	0.322
	C(18)	O(4)	121.100	0.301
O(4)				
	C(19)		1.2140	0.0047

Table A7. Crystal Data and Coordinates of Nonhydrogen Atoms for **167**

$C_{19}H_{13}N_3O_4$, MW=347, monoclinic space group $P2_1/n$, a=13.125(2), b=8.190(3), c=15.872(2)Å, β=110.92(1)° ,Z=4, D_c=1.446gcm^{-3}, μ(MoKα), R=0.044 for 1549 observations, 1°<θ<22.57°, 288 variables.

ATOM	X	Y	Z	U	
N(1)	153(2)	2842(3)	2193(2)	42(1)	*
C(1)	-149(3)	1345(4)	1865(2)	42(1)	*
C(2)	3(3)	-5(5)	2415(3)	56(2)	*
C(3)	453(4)	207(5)	3324(3)	67(2)	*
C(4)	698(3)	1759(5)	3677(3)	59(2)	*
C(5)	543(3)	3054(4)	3082(2)	42(1)	*
C(6)	720(3)	4835(4)	3391(2)	45(1)	*
O(1)	1171(3)	4810(4)	4335(2)	62(1)	*
O(2)	1386(2)	5713(3)	3016(1)	47(1)	*
C(7)	2454(3)	5055(7)	3197(3)	68(2)	*
C(8)	-396(3)	5695(4)	3040(2)	45(1)	*
C(9)	-939(4)	6164(5)	3602(3)	68(2)	*
C(10)	-1952(4)	6866(6)	3228(4)	85(2)	*
C(11)	-2430(4)	6998(5)	2302(4)	72(2)	*
C(12)	-1850(3)	6458(4)	1788(2)	48(1)	*
N(2)	-828(2)	5870(3)	2151(2)	43(1)	*
C(13)	-2324(3)	6444(5)	771(3)	56(2)	*
O(3)	-3065(2)	7368(4)	365(2)	87(1)	*
C(14)	-1861(3)	5268(5)	290(2)	46(1)	*
C(15)	-1703(3)	5655(6)	-506(3)	61(2)	*
C(16)	-1206(4)	4528(6)	-877(3)	69(2)	*
C(17)	-884(3)	3057(6)	-455(2)	58(2)	*
C(18)	-1078(3)	2754(4)	333(2)	46(1)	*
N(3)	-1564(2)	3826(4)	699(2)	42(1)	*
C(19)	-692(3)	1212(5)	861(2)	51(1)	*
O(4)	-831(2)	-109(3)	490(2)	72(1)	*

* EQUIVALENT ISOTROPIC TEMPERATURE FACTOR

INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY, VOL. 4, 316.

Table A8. Bond Distances (Å) and Angles (°) for **115**

Bonds	Å	Angles	°
N1-C1	1.338(2)	C1-N1-C5	116.7(2)
N1-C5	1.335(1)	C7-N2-C11	118.6(2)
N2-C7	1.332(2)	C13-N3-C17	117.9(2)
N2-C11	1.331(2)	N1-C1-C2	123.7(3)
N3-C13	1.333(2)	N1-C1-C18	116.3(2)
N3-C17	1.342(2)	C2-C1-C18	120.0(2)
C1-C2	1.384(2)	C1-C2-C3	118.5(2)
C2-C3	1.369(2)	C2-C3-C4	118.9(2)
C3-C4	1.387(2)	C3-C4-C5	118.4(2)
C4-C5	1.378(2)	N1-C5-C4	123.7(2)
C5-C6	1.515(2)	N1-C5-C6	117.3(2)
C6-O1	1.215(2)	C4-C5-C6	118.9(2)
C6-C7	1.500(2)	O1-C6-C5	120.1(2)
C7-C8	1.391(2)	O1-C6-C7	121.6(2)
C8-C9	1.374(3)	C5-C6-C7	118.2(2)
C9-C10	1.370(3)	N2-C7-C6	115.9(2)
C10-C11	1.388(2)	N2-C7-C8	122.7(2)
C11-C12	1.505(2)	C6-C7-C8	121.4(2)
C12-O2	1.220(2)	C7-C8-C9	118.1(2)
C12-C13	1.513(2)	C8-C9-C10	119.6(2)
C13-C14	1.385(2)	C9-C10-C11	119.0(2)
C14-C15	1.376(3)	N2-C11-C10	122.0(2)
C15-C16	1.380(2)	N2-C11-C12	117.6(2)
C17-C18	1.498(2)	C10-C11-C12	120.3(2)
C18-C1	1.507(2)	O2-C12-C11	120.1(2)
C18-O3	1.218(2)	O2-C12-C13	118.8(2)
		C11-C12-C13	120.9(2)
		N3-C13-C12	118.3(2)
		N3-C13-C14	122.5(2)
		C12-C13-C14	119.2(2)
		C13-C14-C15	118.8(2)
		C14-C15-C16	119.5(3)
		C15-C16-C17	118.0(2)
		N3-C17-C16	123.2(2)
		N3-C17-C18	115.5(2)
		C16-C17-C18	121.3(2)
		O3-C18-C1	120.4(2)
		O3-C18-C17	121.3(2)
		C1-C18-C17	118.3(2)

Table A9. Crystal Data and Coordinates of Nonhydrogen Atoms for 115

$C_{18}H_9N_3O_3$, MW=315.3, monoclonic, $P2_1/c$, a=16.758(2), b=3.8141(4), c=21.357(3)Å, β=91.225(11)°, Z=4, D_c=1.534gcm^{-3}, R=0.042 for 1541 observed data with 1°<θ<25°, MoKα.

Atom	x	y	z	B or Beq
O1	0.64105(10)	0.3932(6)	0.27001(8)	5.26(5)
O2	0.63058(9)	-0.4298(5)	-0.02261(8)	4.45(4)
O3	0.98023(9)	0.2999(6)	0.10191(8)	5.41(5)
N1	0.7962(1)	0.2498(6)	0.17009(8)	2.83(4)
N2	0.6593(1)	-0.0081(6)	0.12282(8)	3.24(5)
N3	0.7937(1)	-0.0515(6)	0.05657(8)	2.79(4)
C1	0.8728(1)	0.1532(7)	0.1673(1)	2.91(5)
C2	0.9155(1)	0.0104(8)	0.2173(1)	3.42(6)
C3	0.8776(1)	-0.0363(8)	0.2728(1)	3.79(6)
C4	0.7974(1)	0.0489(8)	0.2762(1)	3.65(6)
C5	0.7596(1)	0.1874(7)	0.2239(1)	2.92(5)
C6	0.6704(1)	0.2511(8)	0.2251(1)	3.32(6)
C7	0.6198(1)	0.1161(7)	0.1715(1)	2.89(5)
C8	0.5370(1)	0.1110(8)	0.1743(1)	3.43(6)
C9	0.4948(1)	-0.0326(8)	0.1247(1)	3.69(6)
C10	0.5350(1)	-0.1599(8)	0.0743(1)	3.40(6)
C11	0.6177(1)	-0.1396(7)	0.0745(1)	2.83(5)
C12	0.6632(1)	-0.2512(7)	0.0179(1)	3.02(5)
C13	0.7466(1)	-0.1158(7)	0.0069(1)	2.81(5)
C14	0.7697(1)	-0.0466(8)	-0.0538(1)	3.66(6)
C15	0.8441(1)	0.0935(8)	-0.0631(1)	3.86(6)
C16	0.8925(1)	0.1749(7)	-0.0121(1)	3.40(6)

Table A9. (Cont'd)

Atom	x	y	z	B or Beq
C17	0.8644(1)	0.1027(7)	0.0469(1)	2.81(5)
C18	0.9117(1)	0.1963(7)	0.1048(1)	3.25(6)
H2	0.974(1)	-0.044(6)	0.2078(9)	4.1(5)
H3	0.981(1)	-0.126(7)	0.3099(10)	4.6(6)
H4	0.767(1)	0.014(6)	0.3115(8)	2.7(5)
H8	0.514(1)	0.194(6)	0.2106(8)	3.2(5)
H9	0.432(1)	-0.038(7)	0.1279(11)	6.0(7)
H10	0.510(1)	-0.247(6)	0.0379(9)	3.3(5)
H14	0.730(1)	-0.097(7)	-0.0894(10)	4.7(6)
H15	0.862(1)	0.152(6)	-0.1093(9)	3.9(5)
H16	0.944(1)	0.281(6)	-0.0167(9)	3.5(5)

Table A10. Bond Distances (Å) for **120**

Bonds	Conformer 1	Conformer 2
O1-C1	1.220(4)	1.225(5)
O2-C7	1.390(4)	1.417(4)
O2-C19	1.408(6)	1.447(5)
O3-C7	1.434(4)	1.419(4)
O3-C20	1.428(5)	1.403(5)
O4-C13	1.418(4)	1.429(4)
O4-C21	1.417(5)	1.426(5)
O5-C13	1.418(3)	1.419(4)
O5-C22	1.434(4)	1.428(5)
N1-C2	1.344(4)	1.341(4)
N1-C6	1.335(4)	1.333(4)
N2-C8	1.333(4)	1.339(4)
N2-C12	1.336(4)	1.334(4)
N3-C14	1.336(4)	1.343(4)
N3-C18	1.331(4)	1.329(5)
C1-C2	1.507(5)	1.493(5)
C1-C18	1.506(5)	1.493(5)
C2-C3	1.385(4)	1.388(4)
C3-C4	1.361(5)	1.359(5)
C4-C5	1.392(5)	1.381(5)
C5-C6	1.380(4)	1.384(4)
C6-C7	1.521(4)	1.522(4)
C7-C8	1.514(4)	1.533(5)
C8-C9	1.392(4)	1.395(5)
C9-C10	1.368(5)	1.374(5)
C10-C11	1.379(5)	1.371(6)
C11-C12	1.392(4)	1.388(5)
C12-C13	1.515(4)	1.526(5)
C13-C14	1.538(4)	1.523(5)
C14-C15	1.381(4)	1.391(5)
C15-C16	1.390(6)	1.383(7)
C16-C17	1.379(6)	1.378(6)
C17-C18	1.385(4)	1.389(5)
C19-C20	1.532(8)	1.490(7)
C21-C22	1.511(5)	1.496(6)

Table A11. Bond Angles (°) for **120**

Angles	Conformer 1	Conformer 2
C7-O2-C19	111.0(3)	104.0(3)
C7-O3-C20	105.1(3)	108.1(3)
C13-O4-C21	108.0(2)	107.7(3)
C13-O5-C22	105.1(2)	107.1(3)
C2-N1-C6	117.3(2)	117.7(3)
C8-N2-C12	118.5(2)	118.2(3)
C14-N3-C18	118.6(2)	118.1(3)
O1-C1-C2	121.8(3)	120.4(3)
O1-C1-C18	121.8(3)	121.5(3)
C2-C1-C18	116.0(3)	118.0(3)
N1-C2-C1	115.4(3)	115.7(3)
N1-C2-C3	123.0(3)	122.9(3)
C1-C2-C3	121.4(3)	121.4(3)
C2-C3-C4	119.0(3)	118.4(3)
C3-C4-C5	118.6(3)	119.8(3)
C4-C5-C6	118.9(3)	118.4(3)
N1-C6-C5	122.9(3)	122.7(3)
N1-C6-C7	114.8(2)	114.3(3)
C5-C6-C7	122.3(3)	122.4(3)
O2-C7-O3	104.9(3)	106.4(2)
O2-C7-C6	111.4(2)	110.9(3)
O2-C7-C8	109.7(3)	112.5(2)
O3-C7-C6	109.8(3)	109.3(2)
O3-C7-C8	106.7(2)	110.8(3)
C6-C7-C8	113.9(2)	107.0(2)
N2-C8-C7	116.9(3)	114.5(3)
N2-C8-C9	122.5(3)	122.5(3)
C7-C8-C9	120.6(3)	122.4(3)
C8-C9-C10	118.4(3)	118.1(3)
C9-C10-C11	119.8(3)	119.8(4)
C10-C11-C12	118.3(3)	118.7(3)
N2-C12-C11	122.2(3)	122.4(3)
N2-C12-C13	115.2(2)	115.1(3)

Table A11. (Cont'd)

Angles	Conformer 1	Conformer 2
C11-C12-C13	122.3(3)	122.4(3)
O4-C13-O5	106.1(2)	106.6(3)
O4-C13-O5	110.6(2)	109.1(3)
O4-C13-C14	110.3(2)	108.8(3)
O5-C13-C12	109.6(2)	109.5(3)
O5-C13-C14	110.9(2)	109.4(3)
C12-C13-C14	109.3(2)	113.2(3)
N3-C14-C13	115.0(2)	116.0(3)
N3-C14-C15	122.1(3)	122.6(3)
C13-C14-C15	122.7(3)	121.4(3)
C14-C15-C16	118.6(3)	117.6(3)
C15-C16-C17	119.5(3)	120.5(4)
C16-C17-C18	117.7(3)	117.4(4)
N3-C18-C1	115.5(3)	115.7(3)
N3-C18-C17	123.3(3)	123.4(3)
C1-C18-C17	121.3(3)	120.8(3)
O2-C19-C20	103.5(3)	106.0(3)
O3-C20-C19	103.5(4)	105.3(4)
O4-C21-C22	105.7(3)	102.1(3)
O5-C22-C21	102.6(3)	102.6(3)

Table A12. Crystal Data and Coordinates of Nonhydrogen Atoms for 120 (Conformer 1)

$C_{22}H_{17}N_3O_5$, MW=403.4, triclinic group P1, a=10.3233(12), b=11.209(3), c=16.233(2)Å, α=81.939(16), β=89.056(10), γ=88.536(15)°, Z=4, D_c=1.441cm^{-3}, R=0.066 for 5690 observed reflections (2°<θ<75°, CuKα, 542 variables)

Atom	x	y	z	Beq
O1	0.1186(3)	0.1417(4)	0.4720(2)	10.2(1)
O2	0.5379(3)	0.3624(3)	0.1443(2)	6.03(7)
O3	0.5048(3)	0.1649(2)	0.1778(2)	6.04(6)
O4	0.7652(2)	0.2861(2)	0.5422(1)	4.62(5)
O5	0.6163(2)	0.4247(2)	0.4862(1)	3.34(4)
N1	0.3522(2)	0.2269(2)	0.3211(2)	3.43(5)
N2	0.6033(2)	0.2995(2)	0.3450(2)	3.26(5)
N3	0.4371(2)	0.2347(2)	0.4811(2)	3.34(5)
C1	0.2252(3)	0.1754(3)	0.4465(2)	4.57(7)
C2	0.2435(3)	0.2511(3)	0.3629(2)	3.86(6)
C3	0.1573(3)	0.3439(3)	0.3347(2)	4.64(7)
C4	0.1867(3)	0.4190(3)	0.2638(2)	5.13(8)
C5	0.3026(3)	0.3993(3)	0.2222(2)	4.35(7)
C6	0.3814(3)	0.3024(3)	0.2526(2)	3.48(6)
C7	0.5107(3)	0.2758(3)	0.2120(2)	3.78(6)
C8	0.6235(3)	0.2626(3)	0.2712(2)	3.44(6)
C9	0.7409(3)	0.2112(3)	0.2491(2)	4.29(7)
C10	0.8388(3)	0.1983(3)	0.3057(2)	4.66(8)
C11	0.8171(3)	0.2294(3)	0.3841(2)	4.22(7)
C12	0.6965(3)	0.2791(3)	0.4017(2)	3.33(6)
C13	0.6574(3)	0.3026(3)	0.4885(2)	3.33(6)
C14	0.5487(3)	0.2170(3)	0.5221(2)	3.39(6)
C15	0.5674(4)	0.1231(3)	0.5858(2)	4.71(8)
C16	0.4660(4)	0.0454(3)	0.6083(2)	5.9(1)
C17	0.3521(4)	0.0608(3)	0.5646(2)	5.28(9)
C18	0.3432(3)	0.1560(3)	0.5004(2)	3.89(7)
C19	0.5006(5)	0.3243(5)	0.0693(3)	8.6(1)
C20	0.4508(5)	0.1971(5)	0.0971(3)	8.2(1)
C21	0.7596(3)	0.3786(3)	0.5935(2)	5.06(8)
C22	0.6388(3)	0.4527(3)	0.5682(2)	4.11(7)

Table A13. Crystal Data and Coordinates of Nonhydrogen Atoms for 120 (Conformer 2)

$C_{22}H_{17}N_3O_5$, MW=403.4, triclinic group P1, a=10.3233(12), b=11.209(3), c=16.233(2)Å, α=81.939(16), β=89.056(10), γ=88.536(15)°, Z=4, D_c=1.441gcm^{-3}, R=0.066 for 5690 observed reflections (2°<θ<75°, CuKα, 542 variables)

Atom	x	y	z	Beq
O1'	1.1169(3)	0.2409(3)	1.1161(2)	7.95(8)
O2'	0.6489(2)	0.3120(2)	0.8829(2)	4.82(5)
O3'	0.5823(2)	0.1208(2)	0.8816(2)	6.01(6)
O4'	1.0667(2)	0.4201(2)	0.6873(2)	5.50(6)
O5'	1.2113(2)	0.2659(2)	0.7267(2)	5.52(6)
N1'	0.8648(2)	0.2161(2)	0.9795(2)	3.83(5)
N2'	0.8840(2)	0.2541(2)	0.8031(2)	3.64(5)
N3'	1.0918(2)	0.2921(2)	0.9020(2)	3.88(6)
C1'	1.0615(3)	0.2474(3)	1.0493(2)	5.03(8)
C2'	0.9456(3)	0.1733(3)	1.0410(2)	3.90(7)
C3'	0.9269(3)	0.0648(3)	1.0922(2)	4.61(7)
C4'	0.8212(4)	0.0002(3)	1.0796(2)	4.93(8)
C5'	0.7393(3)	0.0401(3)	1.0146(2)	4.53(8)
C6'	0.7653(3)	0.1484(3)	0.9657(2)	3.76(6)
C7'	0.6939(3)	0.1911(3)	0.8852(2)	4.21(7)
C8'	0.7882(3)	0.1749(3)	0.8134(2)	4.01(7)
C9'	0.7852(3)	0.0755(3)	0.7706(2)	5.05(8)
C10'	0.8852(4)	0.0592(3)	0.7160(3)	5.76(9)
C11'	0.9879(4)	0.1354(3)	0.7092(2)	5.25(9)
C12'	0.9848(3)	0.2314(3)	0.7547(2)	3.87(7)
C13'	1.0941(3)	0.3212(3)	0.7506(2)	4.28(7)
C14'	1.1136(3)	0.3697(3)	0.8325(2)	4.19(7)
C15'	1.1547(4)	0.4865(3)	0.8342(3)	5.69(9)
C16'	1.1765(4)	0.5213(4)	0.9112(3)	6.7(1)
C17'	1.1502(3)	0.4445(3)	0.9832(3)	5.72(9)
C18'	1.1050(3)	0.3312(3)	0.9749(2)	4.51(7)
C19'	0.5348(4)	0.3192(5)	0.8317(3)	7.3(1)
C20'	0.4862(4)	0.1941(5)	0.8385(4)	9.3(1)
C21'	1.1537(4)	0.4103(4)	0.6192(3)	6.5(1)
C22'	1.2691(4)	0.3477(4)	0.6619(3)	6.6(1)

Anisotropically refined atoms are given in the form of the equivalent isotropic thermal parameter defined as:
(4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table A14. Important Torsion Angles (°) for 120

	Conformer 1	Conformer 2
C6-N1-C2-C1	-170.9(3)	175.0(3)
C2-N1-C6-C7	175.4(3)	-168.8(3)
C12-N2-C8-C7	174.0(3)	165.9(3)
C8-N2-C12-C13	-169.3(3)	-176.0(3)
C18-N3-C14-C13	172.6(3)	-178.6(3)
C14-N3-C18-C1	-174.7(3)	171.6(3)
O1-C1-C2-N1	-143.1(4)	156.0(4)
C18-C1-C2-N1	43.7(4)	-22.3(5)
O1-C1-C18-N3	-153.6(4)	145.7(4)
C2-C1-C18-N3	19.7(5)	-36.0(4)
N1-C6-C7-O2	-176.2(3)	-56.7(4)
N1-C6-C7-O3	68.1(4)	-173.6(3)
N1-C6-C7-C8	-51.6(4)	66.3(3)
O2-C7-C8-N2	112.1(3)	49.4(4)
O3-C7-C8-N2	-134.8(3)	168.3(3)
C6-C7-C8-N2	-13.5(4)	-72.6(3)
N2-C12-C13-O4	-176.1(3)	-86.5(4)
N2-C12-C13-O5	-59.5(3)	157.2(3)
N2-C12-C13-C14	62.3(3)	34.8(4)
O4-C13-C14-N3	172.8(3)	155.9(3)
O5-C13-C14-N3	55.6(3)	-88.0(3)
C12-C13-C14-N3	-65.4(3)	34.4(4)

Table A15. Bond Distances (Å) and Angles (°) for 119

Bonds	Å	Angles	°
O1-C6	1.226(8)	C12-O3-C19	106.6(4)
O2-C18	1.219(8)	C12-O4-C20	104.8(4)
O3-C12	1.414(6)	C1-N1-C5	117.2(4)
O3-C19	1.424(8)	C7-N2-C11	117.7(5)
O4-C12	1.398(6)	C13-N3-C17	117.8(5)
O4-C20	1.409(7)	N1-C1-C2	122.0(7)
N1-C1	1.338(7)	N1-C1-C18	116.2(5)
N1-C5	1.337(7)	C2-C1-C18	121.8(6)
N2-C7	1.352(8)	C1-C2-C3	120.2(8)
N2-C11	1.336(6)	C2-C3-C4	118.0(6)
N3-C13	1.337(7)	C3-C4-C5	118.9(8)
N3-C17	1.341(8)	N1-C5-C4	123.6(7)
C1-C2	1.388(9)	N1-C5-C6	115.1(5)
C1-C18	1.511(9)	C4-C5-C6	121.3(7)
C2-C3	1.37(1)	O1-C6-C5	120.0(7)
C3-C4	1.38(1)	O1-C6-C7	121.7(7)
C4-C5	1.378(9)	C5-C6-C7	118.3(5)
C5-C6	1.510(9)	N2-C7-C6	116.9(6)
C6-C7	1.475(9)	N2-C7-C8	122.2(6)
C7-C8	1.38(1)	C6-C7-C8	120.8(7)
C8-C9	1.35(1)	C7-C8-C9	118.7(8)
C9-C10	1.38(1)	C8-C9-C10	121.0(7)
C10-C11	1.396(8)	C9-C10-C11	116.9(7)
C11-C12	1.557(8)	N2-C11-C10	123.1(6)
C12-C13	1.517(9)	N2-C11-C12	114.9(5)
C13-C14	1.398(8)	C10-C11-C12	121.6(5)
C14-C15	1.38(1)	O3-C12-O4	107.8(4)
C15-C16	1.37(1)	O3-C12-C11	109.2(5)
C16-C17	1.39(1)	O3-C12-C13	110.8(5)
C17-C18	1.479(9)	O4-C12-C11	111.0(5)
C19-C20	1.480(9)	O4-C12-C13	110.5(5)
		C11-C12-C13	107.4(4)
		N3-C13-C12	114.3(5)
		N3-C13-C14	123.3(6)
		C12-C13-C14	122.2(6)
		C13-C14-C15	117.5(7)
		C14-C15-C16	119.9(7)
		C15-C16-C17	119.1(7)
		N3-C17-C16	122.3(7)
		N3-C17-C18	115.8(5)
		C16-C17-C18	121.9(7)
		O2-C18-C1	118.8(7)
		O2-C18-C17	121.6(7)
		C1-C18-C17	119.6(5)
		O3-C19-C20	105.3(5)
		O4-C20-C19	106.3(6)

Table A16. Crystal Data and Coordinates of Nonhydrogen Atoms for 119

$C_{20}H_{13}N_3O_4$, MW=359.3, orthorhobic space group $Pna2_1$, a=6.8766(15), b=15.5581(9), c=15.5474(16)Å, Z=4, D_c=1.435gcm^{-3}, R=0.042 for 1413 observed reflections (2°<θ<75°, CuKα, 280 variables)

Atom	x	y	z	Beq
O1	0.7078(7)	0.1779(2)	0	9.7(1)
O2	0.6150(6)	0.1190(3)	0.4359(2)	9.3(1)
O3	1.2293(4)	-0.1565(1)	0.2017(2)	6.04(7)
O4	1.3024(4)	-0.0159(1)	0.2241(2)	4.83(6)
N1	0.7233(4)	0.1275(2)	0.2178(2)	4.27(6)
N2	0.9750(5)	0.0320(2)	0.1242(2)	4.39(7)
N3	0.9338(5)	0.0069(2)	0.3025(2)	4.48(7)
C1	0.7093(6)	0.1614(3)	0.2966(3)	4.97(9)
C2	0.7002(7)	0.2495(3)	0.3100(3)	6.7(1)
C3	0.7104(7)	0.3048(2)	0.2418(4)	7.6(1)
C4	0.7329(6)	0.2703(2)	0.1609(4)	6.4(1)
C5	0.7394(6)	0.1823(2)	0.1519(3)	4.92(9)
C6	0.7645(7)	0.1408(3)	0.0648(3)	6.0(1)
C7	0.8492(6)	0.0537(3)	0.0610(3)	5.13(9)
C8	0.7925(7)	-0.0038(3)	-0.0021(3)	6.8(1)
C9	0.8536(9)	-0.0861(4)	0.0035(4)	8.1(1)
C10	0.9711(8)	-0.1129(3)	0.0707(3)	6.4(1)
C11	1.0312(6)	-0.0501(2)	0.1291(3)	4.46(8)
C12	1.1490(6)	-0.0735(2)	0.2114(3)	4.62(8)
C13	1.0093(6)	-0.0707(2)	0.2868(3)	4.56(8)

Table A16. (Cont'd)

Atom	x	y	z	Beq
C14	0.9529(8)	-0.1448(3)	0.3311(3)	6.2(1)
C15	0.8118(8)	-0.1363(3)	0.3936(3)	7.4(1)
C16	0.7300(8)	-0.0577(3)	0.4089(3)	7.1(1)
C17	0.7916(7)	0.0127(3)	0.3612(3)	5.3(1)
C18	0.7001(7)	0.0982(3)	0.3704(3)	5.9(1)
C19	1.4252(8)	-0.1450(3)	0.1743(4)	7.7(1)
C20	1.4592(7)	-0.0511(3)	0.1777(4)	7.3(1)

Table A17. Important Torsion Angles (°) for **119**

C5-N1-C1-C18	-177.4(4)
C1-N1-C5-C6	177.2(4)
C11-N2-C7-C6	170.5(4)
C7-N2-C11-C12	-170.7(4)
C17-N3-C13-C12	172.1(4)
C13-N3-C17-C18	-174.4(4)
N1-C1-C18-O2	-151.7(5)
N1-C1-C18-C17	27.5(6)
N1-C5-C6-O1	151.9(5)
N1-C5-C6-C7	-25.1(6)
O1-C6-C7-N2	154.0(5)
C5-C6-C7-N2	-29.1(6)
N2-C11-C12-O3	-169.4(3)
N2-C11-C12-O4	-50.7(5)
N2-C11-C12-C13	70.3(4)
O3-C12-C13-N3	177.2(4)
O4-C12-C13-N3	57.7(5)
C11-C12-C13-N3	-63.6(5)
N3-C17-C18-O2	-157.6(5)
N3-C17-C18-C1	23.2(6)

Table A18. Bond Distances (Å) for **150**

Bonds	Conformer 1	Conformer 2
O1-C7	1.215(5)	1.229(5)
O2-C13	1.220(5)	1.219(5)
N1-C2	1.340(5)	1.334(5)
N1-C6	1.341(5)	1.339(5)
N2-C8	1.334(5)	1.347(5)
N2-C12	1.331(5)	1.332(6)
N3-C14	1.336(5)	1.331(5)
N3-C18	1.335(5)	1.327(5)
C1-C1	1.531(8)	1.556(8)
C1-C2	1.516(6)	1.522(6)
C1-C18	1.524(6)	1.529(6)
C2-C3	1.388(6)	1.383(6)
C3-C4	1.369(6)	1.374(6)
C4-C5	1.371(6)	1.382(6)
C5-C6	1.368(6)	1.387(6)
C6-C7	1.510(6)	1.497(6)
C7-C8	1.486(6)	1.487(6)
C8-C9	1.390(6)	1.373(6)
C9-C10	1.373(6)	1.357(7)
C10-C11	1.382(6)	1.381(8)
C11-C12	1.391(6)	1.365(7)
C12-C13	1.486(6)	1.510(6)
C13-C14	1.498(6)	1.493(6)
C14-C15	1.387(6)	1.377(6)
C15-C16	1.380(6)	1.377(7)
C16-C17	1.378(6)	1.379(7)
C17-C18	1.372(6)	1.389(6)

Table A19. Bond Angles (°) for 150

Angles	Conformer 1	Conformer 2
C1-C1-C2	111.5(5)	110.6(5)
C1-C1-C8	112.1(5)	109.9(5)
C2-C1-C18	108.0(4)	110.6(4)
C2-N1-C6	117.8(4)	118.3(4)
C8-N2-C12	118.2(4)	116.8(5)
C14-N3-C18	118.0(4)	119.2(5)
C2-C1-C18	108.0(4)	110.6(4)
N1-C2-C1	114.5(4)	116.6(5)
N1-C2-C3	121.7(5)	122.0(5)
C1-C2-C3	123.8(5)	121.4(5)
C2-C3-C4	119.1(5)	119.0(5)
C3-C4-C5	119.4(5)	119.9(5)
C4-C5-C6	118.6(5)	117.3(5)
N1-C6-C5	123.0(5)	123.2(5)
N1-C6-C7	116.9(4)	116.5(5)
C5-C6-C7	120.1(5)	120.2(5)
O1-O7-C6	119.9(5)	120.4(5)
O1-C7-C8	121.1(5)	119.9(5)
C6-C7-C8	118.5(4)	119.7(5)
N2-C8-C7	117.1(4)	116.7(5)
N2-C8-C9	122.4(5)	122.5(5)
C7-C8-C9	120.4(5)	120.8(6)
C8-C9-C10	118.9(5)	119.5(6)
C9-C10-C11	119.3(5)	118.9(6)
C10-C11-C12	118.1(5)	118.4(6)
N2-C12-C11	123.0(5)	123.7(6)
N2-C12-C13	116.4(4)	118.1(5)
C11-C12-C13	120.6(5)	118.2(6)
O2-C13-C12	120.8(5)	119.4(6)
O2-C13-C14	120.1(5)	121.6(6)
C12-C13-C14	119.0(4)	119.0(5)
N3-C14-C13	116.7(4)	117.0(5)
N3-C14-C15	122.9(4)	122.6(5)
C13-C14-C15	120.4(5)	120.4(5)
C14-C15-C16	117.9(5)	118.6(5)
C15-C16-C17	119.3(5)	118.5(5)
C16-C17-C18	119.0(5)	119.7(5)
N3-C18-C1	115.6(4)	117.4(4)
N3-C18-C17	122.6(5)	121.0(5)
C1-C18-C17	121.6(4)	121.6(5)

Table A20. Crystal Data and Coordinates of Nonhydrogen Atoms for 150 (Conformer 1)

$C_{36}H_{20}N_6O_4$, MW=600.0, triclinic P1, a=8.2009(8), b=10.0829(12), c=17.6076(14)Å, α=91.493(8), β=100.188(8), γ=95.061(10)°, D_c=1.399gcm^{-3}, μ(MoKα)=0.88cm^{-1}, R=0.073 for 2306 data having $I \geq \sigma(I)$, 1°<θ<23°, 416 variables. Two independent molecules lying on centers of symmetry.

Atom	x	y	z
O1	0.7055(5)	0.5882(3)	0.0358(2)
O2	0.6441(5)	0.1714(4)	0.3367(2)
N1	0.6369(5)	0.2406(4)	0.0224(2)
N2	0.6639(5)	0.3417(3)	0.1685(2)
N3	0.6097(5)	0.0722(4)	0.1436(2)
C1	0.5949(5)	0.0016(5)	0.0899(3)
C2	0.6789(6)	0.1316(5)	-0.0117(3)
C3	0.7944(6)	0.1394(5)	-0.0607(3)
C4	0.8679(7)	0.2617(6)	-0.0740(3)
C5	0.8294(6)	0.3732(5)	-0.0372(3)
C6	0.7195(6)	0.3580(5)	0.0127(3)
C7	0.6849(6)	0.4768(5)	0.0592(3)
C8	0.6262(6)	0.4535(4)	0.1334(3)
C9	0.5375(6)	0.5465(5)	0.1641(3)
C10	0.4815(6)	0.5202(5)	0.2316(3)
C11	0.5137(6)	0.4021(5)	0.2669(3)
C12	0.6068(6)	0.3161(5)	0.2333(3)
C13	0.6442(6)	0.1871(5)	0.2682(3)
C14	0.6817(6)	0.0757(4)	0.2180(3)
C15	0.7903(7)	-0.0154(5)	0.2483(3)
C16	0.8288(7)	-0.1111(5)	0.1984(3)
C17	0.7618(6)	-0.1101(5)	0.1208(3)
C18	0.6558(6)	-0.0161(4)	0.0956(3)

Table A20. (Cont'd)

Atom	x	y	z
O1A	-0.0365(5)	0.5774(4)	0.2275(2)
O2A	0.2300(6)	-0.0359(4)	0.3351(3)
N1A	0.2299(5)	0.5124(4)	0.3967(2)
N2A	0.1174(5)	0.2879(4)	0.3073(2)
N3A	0.3436(5)	0.2696(4)	0.4389(2)
C1A	0.4193(5)	0.4782(5)	0.5158(2)
C2A	0.2720(6)	0.5432(4)	0.4722(3)
C3A	0.1841(6)	0.6269(5)	0.5096(3)
C4A	0.0473(6)	0.6778(5)	0.4681(3)
C5A	-0.0036(6)	0.6416(5)	0.3907(3)
C6A	0.0911(6)	0.5567(5)	0.3578(3)
C7A	0.0381(6)	0.5073(5)	0.2755(3)
C8A	0.0807(6)	0.3743(5)	0.2511(3)
C9A	0.0910(7)	0.3457(6)	0.1755(3)
C10A	0.1456(8)	0.2284(7)	0.1563(3)
C11A	0.1944(8)	0.1424(6)	0.2140(3)
C12A	0.1776(6)	0.1760(5)	0.2876(3)
C13A	0.2350(7)	0.0831(5)	0.3507(3)
C14A	0.2963(6)	0.1395(5)	0.4309(3)
C15A	0.3038(7)	0.0582(5)	0.4929(3)
C16A	0.3596(7)	0.1143(5)	0.5668(3)
C17A	0.3977(6)	0.2504(5)	0.5744(3)
C18A	0.3855(6)	0.3264(5)	0.5093(3)

Table A21. Bond Distances (Å) of 151

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
CL1	C19	1.749(7)	C4	C5	1.369(8)
CL2	C19	1.749(6)	C5	C6	1.382(8)
CL3	C19	1.745(7)	C6	C7	1.503(8)
CL4	C20	1.728(8)	C7	C8	1.499(8)
CL5	C20	1.694(9)	C8	C9	1.401(8)
CL6	C20	1.723(8)	C9	C10	1.367(9)
O1	C7	1.216(7)	C10	C11	1.38(1)
O2	C13	1.220(6)	C11	C12	1.405(8)
N1	C2	1.338(6)	C12	C13	1.512(8)
N1	C6	1.340(7)	C13	C14	1.499(7)
N2	C8	1.326(7)	C14	C15	1.400(8)
N2	C12	1.328(7)	C15	C16	1.375(8)
N3	C14	1.331(7)	C16	C17	1.366(8)
N3	C18	1.330(6)	C17	C18	1.407(7)
C1	C1	1.360(7)			
C1	C2	1.503(7)			
C1	C18	1.492(7)			
C2	C3	1.399(7)			
C3	C4	1.380(8)			

Table A22. Bond Angles (°) for 151

Atom 1	Atom 2	Atom 3	Angle
C2	N1	C6	117.7(4)
C8	N2	C12	118.1(5)
C14	N3	C18	119.0(4)
C1	C1	C2	122.3(4)
C1	C1	C18	122.9(4)
C2	C1	C18	114.5(4)
N1	C2	C1	116.4(4)
N1	C2	C3	121.8(5)
C1	C2	C3	121.5(5)
C2	C3	C4	119.0(5)
C3	C4	C5	119.4(5)
C4	C5	C6	118.2(5)
N1	C6	C5	123.8(5)
N1	C6	C7	117.5(4)
C5	C6	C7	118.6(5)
O1	C7	C6	119.8(5)
O1	C7	C8	120.2(5)
C6	C7	C8	120.0(5)
N2	C8	C7	117.6(5)
N2	C8	C9	122.4(5)
C7	C8	C9	119.9(5)
C8	C9	C10	119.5(6)
C9	C10	C11	118.4(6)

Table A22. (Cont'd)

Atom 1	Atom 2	Atom 3	Angle
C10	C11	C12	118.6(5)
N2	C12	C11	122.8(5)
N2	C12	C13	117.1(5)
C11	C12	C13	120.1(5)
O2	C13	C12	119.4(5)
O2	C13	C14	120.9(5)
C12	C13	C14	119.6(4)
N3	C14	C13	118.5(5)
N3	C14	C15	123.0(5)
C13	C14	C15	118.4(5)
C14	C15	C16	117.3(5)
C15	C16	C17	120.4(5)
C16	C17	C18	118.8(5)
N3	C18	C1	116.8(4)
N3	C18	C17	121.3(5)
C1	C18	C17	121.8(4)
CL1	C19	CL2	109.5(3)
CL1	C19	CL3	110.8(4)
CL2	C19	CL3	109.1(3)
CL4	C20	CL5	112.8(5)
CL4	C20	CL6	108.3(5)
CL5	C20	CL6	109.5(4)

Table A23. Crystal Data and Coordinates Nonhydrogen Atoms for 151

$C_{36}H_{18}N_6O_4$ $4CH_2Cl_2$, MW=1076, monoclinic $P2_1/c$, a=7.2001(5), b=10.6962(15), c=29.371(5)Å, β=94.439(8)°, D_c=1.585gcm^{-3}, μ(CuKα)=73.34cm^{-1}, R=0.066 for 2283 data having I>3σ(I), 2°<θ<70°, 317 variables.

Atom	x	y	z	B(Å^2)
CL1	0.3723(3)	0.1283(2)	0.60659(8)	6.72(6)
CL2	0.3665(3)	0.3717(2)	0.64656(7)	6.57(5)
CL3	0.4401(3)	0.3467(2)	0.55315(7)	6.50(5)
CL4	0.5018(4)	0.6480(3)	0.7500(1)	11.45(9)
CL5	0.5354(5)	0.8612(3)	0.6930(1)	14.8(1)
CL6	0.2337(5)	0.6985(3)	0.6783(1)	11.68(9)
O1	0.1927(7)	1.0684(4)	0.4472(2)	6.4(1)
O2	0.1309(6)	0.5913(4)	0.2876(1)	4.9(1)
N1	0.0902(6)	0.7537(4)	0.4680(1)	2.65(9)
N2	0.1447(6)	0.8000(4)	0.3795(1)	2.9(1)
N3	0.0714(6)	0.5639(4)	0.4050(1)	2.49(9)
C1	0.0475(7)	0.5354(5)	0.4856(2)	2.3(1)
C2	0.1232(7)	0.6624(5)	0.4987(2)	2.4(1)
C3	0.2375(8)	0.6810(5)	0.5389(2)	3.3(1)
C4	0.3145(9)	0.7975(6)	0.5475(2)	4.0(1)
C5	0.2876(8)	0.8897(5)	0.5154(2)	3.8(1)
C6	0.1771(8)	0.8633(5)	0.4759(2)	2.9(1)
C7	0.1627(8)	0.9588(5)	0.4383(2)	3.6(1)
C8	0.1154(8)	0.9187(5)	0.3899(2)	3.2(1)
C9	0.0448(9)	1.0059(6)	0.3574(2)	4.6(2)

Table A23. (Cont'd)

Atom	x	y	z	B(Å^2)
C10	-0.0017(9)	0.9679(7)	0.3136(2)	4.9(2)
C11	0.0209(9)	0.8432(6)	0.3029(2)	4.3(1)
C12	0.0953(8)	0.7621(6)	0.3372(2)	3.2(1)
C13	0.1194(8)	0.6248(6)	0.3270(2)	3.2(1)
C14	0.1371(8)	0.5325(5)	0.3655(2)	2.8(1)
C15	0.2280(8)	0.4190(5)	0.3587(2)	3.2(1)
C16	0.2516(8)	0.3391(5)	0.3953(2)	3.5(1)
C17	0.1950(8)	0.3732(5)	0.4369(2)	3.2(1)
C18	0.1028(7)	0.4883(5)	0.4408(2)	2.3(1)
C19	0.3151(8)	0.2854(6)	0.5966(2)	4.0(1)
C20	0.388(1)	0.7661(8)	0.7189(2)	7.0(2)

Table A24. Bond Distances (Å) for 127

Bonds	A	Bonds	A
O1-C6	1.396(2)	C5-C6	1.508(3)
O1-C26	1.433(3)	C6-C7	1.536(3)
O2-C6	1.415(2)	C7-C8	1.358(3)
O2-C27	1.421(3)	C8-C9	1.398(3)
O3-C18	1.396(2)	C9-C10	1.356(3)
O3-C29	1.427(3)	C10-C11	1.414(3)
O4-C18	1.413(2)	C11-C12	1.419(3)
O4-C30	1.430(3)	C12-C13	1.432(3)
N1-C1	1.362(3)	C12-C28	1.419(3)
N1-C5	1.351(3)	C13-C14	1.415(3)
N2-C7	1.354(3)	C14-C15	1.370(3)
N2-C11	1.374(3)	C15-C16	1.380(3)
N3-C13	1.362(3)	C16-C17	1.372(3)
N3-C17	1.351(3)	C17-C18	1.537(3)
N4-C19	1.361(3)	C18-C19	1.505(3)
N4-C23	1.371(3)	C19-C20	1.356(3)
N5-C25	1.151(3)	C20-C21	1.396(3)
N6-C28	1.148(3)	C21-C22	1.353(3)
C1-C2	1.406(3)	C22-C23	1.422(3)
C1-C24	1.429(3)	C23-C24	1.419(3)
C2-C3	1.357(3)	C24-C25	1.422(3)
C3-C4	1.402(3)	C26-C27	1.513(3)
C4-C5	1.363(3)	C29-C30	1.510(3)

Table A25. Bond Angles (°) for 127

Angles	°	Angles	°
C6-O1-C26	104.56(17)	N2-C7-C6	116.47(19)
C6-O2-C27	106.56(17)	N2-C7-C8	121.54(20)
C18-O3-C29	106.08(17)	C6-C7-C8	121.91(20)
C18-O4-C30	105.15(17)	C7-C8-C9	118.63(22)
C1-N1-C5	120.37(20)	C8-C9-C10	120.51(22)
C7-N2-C11	121.34(19)	C9-C10-C11	120.29(22)
C13-N3-C17	120.15(19)	N2-C11-C10	117.70(20)
C19-N4-C23	120.90(19)	N2-C11-C12	120.04(20)
N1-C1-C2	118.66(22)	C10-C11-C12	122.26(21)
N1-C1-C24	119.36(21)	C11-C12-C13	126.81(20)
C2-C1-C24	121.98(21)	C11-C12-C28	116.57(21)
C1-C2-C3	120.49(22)	C13-C12-C28	116.60(21)
C2-C3-C4	119.98(22)	N3-C13-C12	119.77(20)
C3-C4-C5	118.00(22)	N3-C13-C14	118.79(21)
N1-C5-C4	122.47(21)	C12-C13-C14	121.44(21)
N1-C5-C6	115.75(20)	C13-C14-C15	120.02(21)
C4-C5-C6	121.61(21)	C14-C15-C16	120.15(22)
O1-C6-O2	106.62(17)	C15-C16-C17	118.43(22)
O1-C6-C5	110.94(18)	N3-C17-C16	122.46(21)
O1-C6-C7	110.98(17)	N3-C17-C18	115.88(19)
O2-C6-C5	109.46(18)	C16-C17-C18	121.51(21)
O2-C6-C7	109.19(17)	O3-C18-O4	106.99(17)
C5-C6-C7	109.59(18)	O3-C18-C17	111.37(18)
O3-C18-C19	111.04(18)	N4-C23-C24	120.18(20)
O4-C18-C17	109.63(18)	C22-C23-C24	122.40(21)

Table A25. (Cont'd)

Angles	°	Angles	°
O4-C18-C19	109.00(18)	C1-C24-C23	126.70(20)
C17-C18-C19	108.77(18)	C1-C24-C25	117.14(21)
N4-C19-C18	115.80(19)	C23-C24-C25	116.16(21)
N4-C19-C20	121.67(21)	N5-C25-C24	178.41(28)
C18-C19-C20	122.25(21)	O1-C26-C27	103.84(19)
C19-C20-C21	119.18(22)	O2-C27-C26	105.38(19)
C20-C21-C22	119.68(22)	N6-C28-C12	178.37(27)
C21-C22-C23	121.03(22)	O3-C29-C30	105.33(20)
N4-C23-C22	117.42(21)	O4-C30-C29	104.99(19)

Table A26. Crystal Data and Coordinates of Nonhydrogen Atoms for 127

$C_{30}H_{22}N_6O_4 \cdot 1/2CH_2Cl_2$, triclinic $P\bar{1}$, a=11.417(2), b=11.556(2), c=11.982(2)Å, α=104.36(2), β=105.58(1), γ=111.69(1)°, Z=2, R=0.053 for 2661 observed data (1°<θ<30°), MoKα radiation, λ=0.71073Å. The DCM solvent molecule is disordered.

Atom	x	y	z
O1	0.6673(2)	1.2237(2)	0.3853(1)
O2	0.5818(2)	1.1885(2)	0.4479(2)
O3	0.7739(2)	1.2808(2)	0.1298(2)
O4	0.8581(2)	1.3254(2)	-0.0144(2)
N1	0.9271(2)	1.3805(2)	0.4672(2)
N2	0.6879(2)	0.9896(2)	0.2588(2)
N3	0.7879(2)	1.0423(2)	0.0781(2)
N4	1.0276(2)	1.3483(2)	0.2943(2)
N5	1.4159(2)	1.5053(2)	0.6725(2)
N6	0.6880(3)	0.5882(2)	0.0239(2)
C1	1.0599(2)	1.3669(2)	0.5529(2)
C2	1.0854(3)	1.3892(3)	0.6799(2)
C3	0.9794(3)	1.3478(3)	0.7163(2)
C4	0.8434(3)	1.2796(3)	0.6267(2)
C5	0.8224(2)	1.2574(2)	0.5041(2)
C6	0.6885(2)	1.1734(2)	0.4080(2)
C7	0.6514(2)	1.0256(2)	0.3473(2)
C8	0.5985(3)	0.9373(3)	0.3988(2)
C9	0.5810(3)	0.8062(3)	0.3495(3)
C10	0.6163(3)	0.7684(2)	0.2523(2)
C11	0.6723(2)	0.8617(2)	0.2003(2)
C12	0.7186(2)	0.8266(2)	0.0985(2)
C13	0.7647(2)	0.9117(2)	0.0369(2)

Table A26. (Cont'd)

Atom	x	y	z
C14	0.7936(3)	0.8630(2)	-0.0675(2)
C15	0.8441(3)	0.9466(3)	-0.1252(2)
C16	0.8667(3)	1.0786(3)	-0.0817(2)
C17	0.8371(2)	1.1227(2)	0.0194(2)
C18	0.8685(2)	1.2706(2)	0.0788(2)
C19	1.0129(2)	1.3499(2)	0.1782(2)
C20	1.1232(3)	1.4087(2)	0.1517(2)
C21	1.2553(3)	1.4643(3)	0.2442(3)
C22	1.2713(2)	1.4619(2)	0.3595(2)
C23	1.1555(2)	1.4063(2)	0.3891(2)
C24	1.1689(2)	1.4111(2)	0.5116(2)
C25	1.3052(3)	1.4644(2)	0.6015(2)
C26	0.5223(3)	1.1760(3)	0.2441(3)
C27	0.4714(3)	1.1679(3)	0.3476(3)
C28	0.6974(3)	0.6946(3)	0.0557(2)
C29	0.6612(3)	1.2658(3)	0.0285(3)
C30	0.7160(3)	1.2915(3)	-0.0692(3)
C1S	0.0000	0.0566	0.5273
C11	0.0489(3)	0.0203(3)	0.3935(3)
C12	0.0840	0.0293	0.4727
C13	0.0273	-0.0293	0.4160
C14	0.0547	0.0840	0.4160
C15	0.0000	0.0273	0.3594

Table A27. Bond Distances (Å) and Angles (°) for **125**

Bonds	Å	Angles	°
O1-C6	1.212(4)	C1-N1-C5	115.5(3)
O2-C12	1.192(4)	C7-N2-C11	117.6(3)
O3-C18	1.222(4)	C13-N3-C17	115.3(3)
O4-C24	1.216(4)	C19-N4-C23	115.5(3)
N1-C1	1.332(4)	N1-C1-C2	125.2(3)
N1-C5	1.336(4)	N1-C1-C24	115.5(3)
N2-C7	1.351(4)	C2-C1-C24	119.2(3)
N2-C11	1.351(4)	C1-C2-C3	117.9(4)
N3-C13	1.334(4)	C2-C3-C4	118.9(4)
N3-C17	1.340(4)	C3-C4-C5	118.3(3)
N4-C19	1.345(4)	N1-C5-C4	124.0(3)
N4-C23	1.340(4)	N1-C5-C6	115.5(3)
C1-C2	1.379(5)	C4-C5-C6	120.2(3)
C1-C24	1.510(4)	O1-C6-C5	120.3(3)
C2-C3	1.369(6)	O1-C6-C7	120.1(3)
C3-C4	1.386(5)	C5-C6-C7	119.5(3)
C4-C5	1.383(5)	N2-C7-C6	115.0(3)
C5-C6	1.509(5)	N2-C7-C8	121.4(3)
C6-C7	1.481(5)	C6-C7-C8	123.6(3)
C7-C8	1.376(5)	C7-C8-C9	121.5(4)
C8-C9	1.359(6)	C8-C9-C10	117.8(4)
C9-C10	1.388(6)	C9-C10-C11	119.1(4)
C10-C11	1.385(4)	N2-C11-C10	122.6(3)
C11-C12	1.504(5)	N2-C11-C12	116.3(3)
C12-C13	1.508(4)	C10-C11-C12	121.0(3)
C13-C14	1.386(4)	O2-C12-C11	120.4(3)
C14-C15	1.397(5)	O2-C12-C13	123.1(3)
C15-C16	1.361(5)	C11-C12-C13	116.5(3)
C16-C17	1.379(4)	N3-C13-C12	114.3(3)
C17-C18	1.484(4)	N3-C13-C14	125.2(3)
C18-C19	1.506(4)	C12-C13-C14	120.4(3)
C19-C20	1.392(4)	C13-C14-C15	116.6(3)
C20-C21	1.363(5)	C14-C15-C16	119.8(3)
C21-C22	1.363(5)	C15-C16-C17	118.2(3)
C22-C23	1.399(4)	N3-C17-C16	124.7(3)
C23-C24	1.495(4)	N3-C17-C18	115.0(3)
		C16-C17-C18	120.3(3)
		O3-C18-C17	119.9(3)
		O3-C18-C19	120.0(3)
		C17-C18-C19	120.1(3)
		N4-C19-C18	115.2(3)
		N4-C19-C20	124.0(3)
		C18-C19-C20	120.8(3)
		C19-C20-C21	118.7(3)
		C20-C21-C22	119.2(3)
		C21-C22-C23	118.9(4)
		N4-C23-C22	123.6(3)

Table A27. (Cont'd)

Angles	°
N4-C23-C24	114.6(3)
C22-C23-C24	121.8(3)
O4-C24-C1	119.5(3)
O4-C24-C23	120.3(3)
C1-C24-C23	120.2(3)

Table A28. Crystal Data and Coordinates of Nonhydrogen Atoms for 125

$C_{24}H_{12}N_4O_4$, monoclinic space group $P2_1/c$, a=15.932(1), b=11.2384(5), c=11.8585(7)Å, β=110.226(6)°, Z=4, R=0.060 for 2844 observed data (2°<θ<67°), CuKα radiation, λ=1.54184Å.

Atom	x	y	z	Beq
O1	0.54339(2)	-0.03660(6)	0.3358(2)	7.05(5)
O2	0.2689(2)	-0.51248(6)	0.2832(3)	7.87(6)
O3	-0.03735(2)	-0.21166(6)	-0.0586(2)	5.44(4)
O4	0.1952(2)	0.16198(7)	0.4065(2)	6.98(4)
N1	0.3228(1)	0.01600(3)	0.3096(2)	3.73(4)
N2	0.37984(4)	-0.23890(4)	0.3045(2)	3.55(4)
N3	0.16415(2)	-0.29713(8)	0.1362(2)	3.55(3)
N4	0.10489(1)	-0.0471(2)	0.1777(1)	3.53(4)
C1	0.25885(1)	0.09694(6)	0.2648(1)	3.79(4)
C2	0.25736(2)	0.1808(2)	0.1793(2)	5.84(5)
C3	0.32869(1)	0.1851(3)	0.1401(1)	6.05(7)
C4	0.3989(2)	0.10625(3)	0.1885(3)	4.90(5)
C5	0.39147(1)	0.02211(8)	0.2696(1)	3.75(6)
C6	0.46782(2)	-0.0621(3)	0.3287(2)	4.66(4)
C7	0.44981(1)	-0.1764(1)	0.37825(9)	3.73(4)
C8	0.49975(1)	-0.2182(3)	0.4905(1)	5.31(7)
C9	0.4813(1)	-0.3243(2)	0.5317(3)	6.65(5)
C10	0.40941(3)	-0.38921(8)	0.4571(2)	5.30(6)
C11	0.36232(2)	-0.34590(4)	0.3433(2)	3.91(4)
C12	0.28675(1)	-0.41577(8)	0.2571(1)	4.21(4)

Table A28. (Cont'd)

Atom	x	y	z	Beq
C13	0.23691(2)	-0.3572(1)	0.1383(2)	3.57(4)
C14	0.26686(4)	-0.36892(3)	0.0421(2)	4.32(7)
C15	0.21482(1)	-0.3155(2)	-0.0658(1)	4.26(4)
C16	0.13956(8)	-0.25462(4)	-0.0718(2)	4.00(6)
C17	0.1164(2)	-0.24932(2)	0.0298(2)	3.38(6)
C18	0.03152(2)	-0.1916(2)	0.0255(2)	4.04(4)
C19	0.0298(2)	-0.11056(2)	0.1258(3)	3.62(4)
C20	-0.04584(3)	-0.10309(3)	0.1588(2)	4.63(5)
C21	-0.0431(1)	-0.03217(3)	0.2532(3)	5.22(5)
C22	0.03119(1)	0.0350(2)	0.3072(1)	4.92(5)
C23	0.10311(2)	0.02720(3)	0.2655(2)	3.67(4)
C24	0.18649(6)	0.09873(3)	0.3200(3)	4.08(4)

Table A29. Bond Distances (Å) and Angles (°) for 178

CU(1)				
	CL(1)		2.2282	0.0032
	CL(2)		2.2530	0.0033
	N(1)		2.0334	0.0088
	O(1)		2.4679	0.0078
	N(2)		2.0220	0.0080
	N(3)		2.3619	0.0098
	CL(1)	CL(2)	95.468	0.127
	CL(1)	N(1)	88.988	0.242
	CL(1)	O(1)	105.390	0.177
	CL(1)	N(2)	172.568	0.309
	CL(1)	N(3)	101.255	0.233
	CL(2)	N(1)	175.493	0.360
	CL(2)	O(1)	102.468	0.192
	CL(2)	N(2)	91.963	0.253
	CL(2)	N(3)	102.089	0.238
	N(1)	O(1)	76.900	0.324
	N(1)	N(2)	83.582	0.325
	N(1)	N(3)	76.308	0.346
	O(1)	N(2)	72.789	0.303
	O(1)	N(3)	141.503	0.327
	N(2)	N(3)	77.189	0.351
CL(1)				
	CU(1)		2.2282	0.0032
CL(2)				
	CU(1)		2.2530	0.0033
N(1)				
	CU(1)		2.0334	0.0088
	C(12)		1.3507	0.0139
	C(16)		1.3459	0.0158
	C(12)	C(16)	119.693	0.912
C(12)				
	N(1)		1.3507	0.0139
	C(13)		1.3755	0.0153
	C(03)		1.5178	0.0179
	N(1)	C(13)	121.454	1.111
	N(1)	C(03)	120.800	0.920
	C(13)	C(03)	117.730	0.999
C(13)				
	C(12)		1.3755	0.0153
	H(13)		1.0810	0.0162
	C(14)		1.3676	0.0196
	C(12)	H(13)	120.434	1.360
	C(12)	C(14)	119.156	1.079
	H(13)	C(14)	120.410	1.246

Table A29. (Cont'd)

C(14)				
	C(13)		1.3676	0.0196
	H(14)		1.0796	0.0170
	C(15)		1.3696	0.0175
	C(13)	H(14)	119.817	1.343
	C(13)	C(15)	120.643	1.125
	H(14)	C(15)	119.540	1.505
C(15)				
	C(14)		1.3696	0.0175
	H(15)		1.0797	0.0200
	C(16)		1.4132	0.0163
	C(14)	H(15)	120.900	1.279
	C(14)	C(16)	118.250	1.241
	H(15)	C(16)	120.850	1.229
C(16)				
	N(1)		1.3459	0.0158
	C(15)		1.4132	0.0163
	C(01)		1.5311	0.0144
	N(1)	C(15)	120.612	0.975
	N(1)	C(01)	114.516	0.937
	C(15)	C(01)	124.855	1.119
C(01)				
	C(16)		1.5311	0.0144
	O(1)		1.4183	0.0151
	O(2)		1.4038	0.0159
	C(22)		1.5245	0.0127
	C(16)	O(1)	109.709	0.881
	C(16)	O(2)	107.621	0.897
	C(16)	C(22)	110.020	0.885
	O(1)	O(2)	113.355	0.907
	O(1)	C(22)	103.728	0.870
	O(2)	C(22)	112.380	0.894
O(1)				
	CU(1)		2.4678	0.0078
	C(01)		1.4183	0.0151
	C(1)		1.4604	0.0124
	C(01)	C(1)	116.949	0.824
C(1)				
	O(1)		1.4604	0.0124
	H(1A)		1.0901	0.0146
	H(1B)		1.0771	0.0108
	C(2)		1.5109	0.0214
	O(1)	H(1A)	104.712	1.031
	O(1)	H(1B)	119.091	1.078
	O(1)	C(2)	106.376	0.889
	H(1A)	H(1B)	101.962	0.982
	H(1A)	C(2)	116.242	1.148
	H(1B)	C(2)	108.893	1.132

Table A29. (Cont'd)

C(2)				
	C(1)		1.5109	0.0214
	H(2A)		1.0747	0.0124
	H(2B)		1.0999	0.0114
	H(2C)		1.0564	0.0156
	C(1)	H(2A)	109.896	1.149
	C(1)	H(2B)	108.089	1.141
	C(1)	H(2C)	109.589	1.179
	H(2A)	H(2B)	108.433	1.178
	H(2A)	H(2C)	111.092	1.245
	H(2B)	H(2C)	109.684	1.165
O(2)				
	C(01)		1.4038	0.0159
	H(01)		0.8803	0.0079
	H(02)		2.1964	0.0088
	C(01)	H(01)	125.368	0.980
	C(01)	H(02)	104.783	0.715
	H(01)	H(02)	50.285	0.457
N(2)				
	CU(1)		2.0219	0.0080
	C(22)		1.3248	0.0156
	C(26)		1.3672	0.0119
	C(22)	C(26)	118.594	0.887
C(22)				
	C(01)		1.5245	0.0127
	N(2)		1.3248	0.0156
	C(23)		1.3888	0.0165
	C(01)	N(2)	113.548	0.910
	C(01)	C(23)	122.061	1.103
	N(2)	C(23)	124.318	0.914
C(23)				
	C(22)		1.3888	0.0165
	H(23)		1.0805	0.0207
	C(24)		1.3610	0.0157
	C(22)	H(23)	121.762	1.112
	C(22)	C(24)	116.433	1.271
	H(23)	C(24)	121.805	1.265
C(24)				
	C(23)		1.3610	0.0157
	H(24)		1.0794	0.0161
	C(25)		1.3738	0.0212
	C(23)	H(24)	119.203	1.546
	C(23)	C(25)	121.694	1.106
	H(24)	C(25)	119.103	1.268
C(25)				
	C(24)		1.3738	0.0212
	H(25)		1.0810	0.0159
	C(26)		1.4007	0.0164
	C(24)	H(25)	120.678	1.338
	C(24)	C(26)	118.724	1.009
	H(25)	C(26)	120.598	1.519

Table A29. (Cont'd)

C(26)				
	N(2)		1.3672	0.0119
	C(25)		1.4007	0.0164
	C(02)		1.5267	0.0186
	N(2)	C(25)	119.872	1.139
	N(2)	C(02)	119.923	0.943
	C(25)	C(02)	120.203	0.942
C(02)				
	C(26)		1.5267	0.0186
	O(3)		1.2269	0.0120
	C(32)		1.4925	0.0151
	C(26)	O(3)	118.196	1.001
	C(26)	C(32)	120.950	0.866
	O(3)	C(32)	120.665	1.163
O(3)				
	C(02)		1.2269	0.0120
N(3)				
	CU(1)		2.3618	0.0098
	C(32)		1.3500	0.0120
	C(36)		1.3410	0.0129
	C(32)	C(36)	118.197	1.012
C(32)				
	C(02)		1.4925	0.0151
	N(3)		1.3500	0.0120
	C(33)		1.3638	0.0178
	C(02)	N(3)	116.111	1.041
	C(02)	C(33)	121.180	0.871
	N(3)	C(33)	122.708	0.932
C(33)				
	C(32)		1.3638	0.0178
	H(33)		1.0795	0.0142
	C(34)		1.3803	0.0155
	C(32)	H(33)	119.997	1.174
	C(32)	C(34)	119.990	0.968
	H(33)	C(34)	120.014	1.357
C(34)				
	C(33)		1.3803	0.0155
	H(34)		1.0812	0.0192
	C(35)		1.4123	0.0147
	C(33)	H(34)	120.965	1.126
	C(33)	C(35)	118.109	1.177
	H(34)	C(35)	120.927	1.131
C(35)				
	C(34)		1.4123	0.0147
	H(35)		1.0794	0.0140
	C(36)		1.3879	0.0173
	C(34)	H(35)	120.911	1.301
	C(34)	C(36)	118.295	0.936
	H(35)	C(36)	120.795	1.102

Table A29. (Cont'd)

C(36)				
	N(3)		1.3410	0.0129
	C(35)		1.3879	0.0173
	C(03)		1.5101	0.0134
	N(3)	C(35)	122.675	0.871
	N(3)	C(03)	116.955	1.019
	C(35)	C(03)	120.327	0.885
C(03)				
	C(12)		1.5178	0.0179
	C(36)		1.5101	0.0134
	O(4)		1.2041	0.0127
	C(12)	C(36)	119.599	0.862
	C(12)	O(4)	120.090	0.916
	C(36)	O(4)	119.955	1.109
O(4)				
	C(03)		1.2041	0.0127
O(5)				
	C(5)		1.5042	0.0089
	H(02)		1.0800	0.0114
	H(01)		2.2409	0.0095
	H(02)	C(5)	109.468	0.897
	H(01)	C(5)	144.346	0.669
	H(01)	H(02)	50.797	0.403
C(5)				
	O(5)		1.5042	0.0088
	H(5A)		1.0803	0.0001
	H(5B)		1.0804	0.0001
	H(5C)		1.0784	0.0001
	H(5D)		1.0800	0.0001
	C(6A)		0.9922	0.0001
	C(6B)		1.5945	0.0002
	O(5)	H(5A)	109.396	0.407
	O(5)	H(5B)	109.440	0.468
	O(5)	H(5C)	109.203	0.405
	O(5)	H(5D)	109.232	0.404
	O(5)	C(6A)	109.767	0.405
	O(5)	C(6B)	110.395	0.467
	H(5A)	H(5B)	109.387	0.005
	H(5A)	C(6A)	109.409	0.012
	H(5B)	C(6A)	109.428	0.008
	H(5C)	H(5D)	109.470	0.011
	H(5C)	C(6B)	109.274	0.012
	H(5D)	C(6B)	109.252	0.005
	O(5)	C(6B)	110.395	0.467
	C(6A)	C(6B)	111.827	0.020

Table A29. (Cont'd)

C(6A)				
	C(5)		0.9922	0.0001
	H(6A)		1.0800	0.0002
	H(6B)		1.0802	0.0001
	H(6C)		1.0800	0.0001
	C(5)	H(6A)	109.436	0.013
	C(5)	H(6B)	109.476	0.015
	C(5)	H(6C)	109.500	0.005
	H(6A)	H(6B)	109.491	0.012
	H(6A)	H(6C)	109.499	0.011
	H(6B)	H(6C)	109.426	0.015
C(6B)				
	C(5)		1.5945	0.0002
	H(6D)		1.0805	0.0002
	H(6E)		1.0811	0.0001
	H(6F)		1.0800	0.0001
	C(5)	H(6D)	109.486	0.011
	C(5)	H(6E)	109.488	0.008
	C(5)	H(6F)	109.437	0.013
	H(6D)	H(6E)	109.425	0.012
	H(6D)	H(6F)	109.464	0.012
	H(6E)	H(6F)	109.529	0.012

Table A30. Crystal Data and Coordinates of Nonhydrogen Atoms for 178

$C_{22}H_{21}N_3O_5CuCl_2$, MW=541.84, monoclinic $P2_1/c$, a=9.294(5), b=28.014(6), c=9.799(3)Å, β=114.48(4)°, Z=4, D_c=1.549gcm^{-3}, μ(MoKα)=11.32cm^{-1}, R=0.0846 for 2257 observed data (of 4150 unique data), 1°<θ<25°, 284 variables.

ATOM	X	Y	Z	U	
CU(1)	1977.7(14)	1211.5(5)	-96.4(12)	37.2(5)	*
CL(1)	4611.3(31)	1189.3(12)	909.9(32)	60.2(13)	*
CL(2)	1714.8(36)	1452.0(12)	-2382.0(28)	60.4(13)	*
N(1)	2028(9)	988(4)	1897(8)	40(3)	*
C(12)	2812(12)	600(4)	2665(10)	41(4)	*
C(13)	2987(13)	513(5)	4107(11)	51(5)	*
C(14)	2306(15)	818(5)	4757(12)	59(5)	*
C(15)	1427(14)	1199(5)	3974(11)	58(5)	*
C(16)	1299(12)	1279(4)	2504(11)	46(4)	*
C(01)	329(12)	1679(4)	1465(11)	46(5)	*
O(1)	1292(8)	1940(3)	923(7)	46(3)	*
C(1)	2628(14)	2200(5)	2030(12)	61(5)	*
C(2)	3330(15)	2491(5)	1157(14)	71(6)	*
O(2)	-298(9)	1960(3)	2274(9)	70(4)	*
N(2)	-390(9)	1206(3)	-745(8)	39(3)	*
C(22)	-953(12)	1467(4)	51(11)	43(4)	*
C(23)	-2551(13)	1528(5)	-302(14)	57(5)	*
C(24)	-3579(13)	1316(5)	-1586(14)	64(6)	*
C(25)	-3062(13)	1038(5)	-2448(14)	64(6)	*
C(26)	-1434(12)	966(4)	-1970(11)	44(5)	*
C(02)	-823(14)	617(4)	-2804(12)	52(5)	*
O(3)	-1577(10)	574(3)	-4163(8)	74(4)	*
N(3)	1352(10)	392(4)	-491(9)	47(4)	*
C(32)	575(12)	307(4)	-1976(11)	43(5)	*
C(33)	1019(13)	-42(4)	-2692(12)	49(5)	*
C(34)	2313(14)	-325(4)	-1897(13)	57(5)	*
C(35)	3160(12)	-235(4)	-349(12)	47(5)	*
C(36)	2619(12)	123(4)	299(11)	40(4)	*
C(03)	3497(13)	238(4)	1945(11)	45(5)	*
O(4)	4654(9)	12(3)	2708(8)	63(4)	*
O(5)	-1193(12)	2823(4)	1489(10)	103(5)	*
C(5)	-2014	3018	-76	199(11)	
C(6A)	-2044	2771	-813	270(22)	
C(6B)	-3741	3202	-369	270(22)	

* EQUIVALENT ISOTROPIC TEMPERATURE FACTOR

INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY, VOL. 4, 316.

VITA

Young Je Joo was born in Pyung-Yang, Korea, on February 27, 1949. After graduation from Jemulpo High School, he entered Seoul National University, Seoul, Korea, in 1967. In 1972, he received a B.S. in Chemistry, after which he entered the Graduate School at Seoul National University. He worked on the study of carotenoids under the supervision of Professor Tae-Young Lee. From that institute he was awarded a M.S. degree with a major in Organic Chemistry in 1976. That same year he was employed with the Korea Institute of Science and Technology, Seoul, Korea. He began additional graduate work at Washington University in St. Louis, MO, in 1980, and entered the Graduate School at Louisiana State University in August, 1982. The requirements for the doctoral degree were met while working as a graduate assistant in the Chemistry Department at Louisiana State University in Baton Rouge, LA.

DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Young Je Joo

Major Field: Chemistry (Organic)

Title of Dissertation: SYNTHESIS AND CHARACTERIZATION OF CARBON-BRIDGED [1$_n$](2,6)PYRIDINOPHANES

Approved:

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Date of Examination:

November 20, 1987